Neurological Soft Signs, Cognition in Childhood, Attention Deficit Hyperactivity Disorder and Lifetime Major Depressive Disorder

NEUROLOGICAL SOFT SIGNS, COGNITION IN CHILDHOOD, ATTENTION DEFICIT HYPERACTIVITY DISORDER AND LIFETIME MAJOR DEPRESSIVE DISORDER

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Abstract

Background: Neurological soft signs (NSS), subtle but abnormal motor and sensory signs and involuntary movements, have been implicated as risk factors for a number of psychiatric and neurodevelopmental disorders. Prior studies were based on small clinical samples, did not control for important confounding factors or examine domain or age specificity. Here we investigate the associations between NSS and multiple domains of cognitive functioning, Attention Deficit Hyperactivity Disorder (ADHD) and its subtypes and finally with lifetime diagnosis of major depressive disorder (MDD) and its age of onset in a large, population-based cohort, while adjusting for important confounding factors.

Methods: We analyzed data from the Collaborative Perinatal Project (CPP), that followed the offspring of a pregnancy cohort till the age of seven and its follow up project, the New England Family Studies (NEFS) that followed the adult offspring of the Providence and Boston sites of the CPP. We adjusted for a wide array of confounding factors, including demographic variables as well as risk factors for brain injury and aberrant neurodevelopment.

Results: NSS were associated with poor cognitive performance across all domains with no specificity. Each additional soft sign was associated with approximately 4 units drop in any cognitive score. NSS were associated with increased odds of all subtypes of ADHD. Each additional soft sign was associated with 70% increase in the odds of ADHD diagnosis. However,

NSS was not associated with a higher risk of major depressive disorder in childhood compared to adolescence or adulthood.

Conclusions: There is an association between NSS and poor cognitive performance and ADHD that is not attributable to established risk factors for brain injury and aberrant neurodevelopment. Further research should seek the mechanisms for these associations, and finally evaluate the effectiveness of interventions targeting NSS in the assessment and treatment of these childhood conditions.

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Overview

Neurological soft signs (NSS) are neurological abnormalities that are easily detectable during a routine neurological examination. They include poor motor coordination, sensory perceptual difficulties, and involuntary movements. NSS are thought to be manifestations of a minor non-specific cerebral dysfunction (Dazzan & Murray, 2002). Brain injury during the perinatal period or aberrant neurodevelopment may give rise to NSS (Ferriero, 2004; Nichols & Chen, 1981).

NSS have been an area of controversy. Some described them as signs of neuronal immaturity that improve with time and training and have no significant implications on overall functioning (Camp, Bialer, Sverd, & Winsberg, 1978; Foster & Margolin, 1978; Hall & Kramer, 1995), while others found them to be associated with poor cognitive performance (Breslau, Chilcoat, Johnson, Andreski, & Lucia, 2000; Obiols, Serrano, Caparrós, Subirá, & Barrantes, 1999; Semerci, 2000), Attention Deficit Hyperactivity Disorder (ADHD) (Cardo, Casanovas, de la Banda, & Servera, 2008; Patankar, Sangle, Shah, Dave, & Kamath, 2012; Uslu, Kapci Eg Fau - Oztop, & Oztop, 2007) and mood disorders (Piek, Barrett, Smith, Rigoli, & Gasson, 2010; Poole et al., 2016; Shaffer, 1978) among other psychiatric and neurodevelopmental disorders. However, the evidence supporting these associations was based on small or clinical samples, or arbitrary measures of NSS. In addition, prior studies did not adjust adequately for important confounding factors, such as perinatal risk factors.

The objective of this thesis is to study the association between NSS and cognitive functions, ADHD and lifetime major depressive disorder (MDD). To answer these questions, we utilized data from the Collaborative Perinatal Project (CPP), and its follow up project, the New

England Family Studies (NEFS). The CPP is a large multi-site prospective cohort study that recruited 48,197 pregnant women at 12 university-affiliated medical centers between 1959 and 1966. Women were followed through pregnancy and delivery and their offspring were followed for the first 7 years of life (Broman, 1984b; Niswander & Gordon, 1972). The NEFS project is series of follow up studies that were established to locate and interview the adult CPP offspring at the Providence, Rhode Island and Boston, Massachusetts's sites. Each of the follow up studies included structured diagnostic interviews for major depression (n= 2,500) and two of them included structured diagnostic interviews for ADHD (n=2,068) (Gilman, Abrams, & Buka, 2003; Gilman et al., 2008; Loucks et al., 2012).

This thesis offers multiple methodological advantages: a large community sample, prospective design, NSS measure that better reflects the proposed underlying pathology, and finally adjustment for important confounding factors such as perinatal risk factors. In addition, we attempt to answer novel questions specific to these associations, such as a differential effect on cognitive sub-domains, ADHD subtypes and age of onset of MDD.

Our analysis showed that NSS were associated with poor cognitive performance in all domains and with higher rates of all subtypes of ADHD. However, NSS were not associated with MDD or its age of onset.

We examined the association between NSS at age 7 and Wechsler intelligence scale and the Wide Range Achievement Test (WRAT) scores assessed at the same age. Our results showed around 4 units (approximately a 1/3 of the standard deviation) drop in all cognitive scores with each additional soft sign. These results corroborated prior reports on the association (Breslau et al., 2000; Obiols et al., 1999; Semerci, 2000). We observed a greater decline in the verbal compared to the performance domain of Wechsler test and in the spelling compared to arithmetic

and reading domains of the WRAT. This is particularly important when attempting to define associated brain regions or substrates. However, these results should be corroborated as recent reports suggested that, similar to NSS, anatomical correlates of intelligence are distributed throughout the brain (Colom, Jung, & Haier, 2006; Dazzan et al., 2006; Luders, Narr, Thompson, & Toga, 2009). In addition, we found no sex specific difference in the association, after adjusting for brain injury factors that are often hypothesized to cause the sex difference in NSS.

These findings should be interpreted with caution, given the following limitations: 1. Potential measurement error in assessing cognitive functions. However, the WISC and WRAT continue to be the most important components of any modern cognitive testing. 2. While information on confounding factors was collected prospectively, NSS and cognitive performance were assessed at the same point of time. Thus, a temporal association could not be established. However, reverse causation is unlikely.

Our findings on ADHD were similar to prior reports (Cardo et al., 2008; Gillberg, 2003; Patankar et al., 2012; Uslu et al., 2007). Each additional soft sign was associated with 70% increase in the odds of any ADHD diagnosis. We did not find evidence for a differential effect of NSS on ADHD subtypes. Specifically, NSS did not predict the risk of hyperactive subtype compared to other subtypes. Our results support recent evidence on the lack of validity of ADHD subtypes (Faraone, Biederman, Weber, & Russell, 1998; Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005; Lahey, Pelham, Loney, Lee, & Willcutt, 2005).

Our analysis on ADHD has a number of limitations: 1. The NEFS included a number of follow up studies, each of them had different objectives, inclusion and exclusion criteria. This may undermine the representativeness of the sample. However, the prevalence and male: female ratio of ADHD were similar to those reported in community samples (Brown et al., 2001;

Faraone, 2003). In addition, demographics and distribution of NSS and other risk factors were similar to those of the CPP sample. 2. ADHD assessment was collected from the adult offspring retrospectively. However, the frequencies of behavioral ratings suggestive of ADHD, assessed at age 7, were twice as common among those with ADHD diagnosis compared to those without the diagnosis. In addition, there is ample evidence to support the validity of retrospective recall of ADHD symptoms (Faraone, Biederman, Feighner, & Monuteaux, 2000; Glockner-Rist, Pedersen, & Rist, 2013; Murphy & Schachar, 2000).

Our thesis did not find an association between NSS and major depressive disorder. Contrary to our hypothesis, NSS did not predict the risk of MDD in childhood compared to later stages of life. Because of the methodological advantages mentioned above, this analysis provides a strong evidence to corroborate prior reports on the lack of association between NSS and MDD (Boks, Liddle, Burgerhof, Knegtering, & van den Bosch, 2004; Zhao et al., 2013). The lack of association may suggest that NSS and depression are neurobiologically different or that the challenges imposed by NSS are not significant enough to give rise to clinical depression.

Again, a limitation of this analysis was the use of NEFS studies' sample. Although the distribution of NSS and some risk factors were similar to those found in general population, the prevalence of MDD in this sample was higher than rates reported in other epidemiological studies (Kessler, Berglund, Demler, & et al., 2003). This undermines the representativeness of this sample compared to the general population.

A general limitation in this thesis is potential error in measuring NSS. However, our measure of NSS is comparable to modern batteries used in research. NSS were assessed during a neurological examination performed by trained clinicians; such exam is equivalent to contemporary practice.

This thesis used data from the CPP and its follow up studies. Other than being an old study with some outdated measures, the CPP was criticized at the time for undirected data collection and lack of statistical representativeness of its sample. However, the quality, completeness and consistency of the data are remarkably rigorous by today's standards (Hardy, 2003; Klebanoff, 2009). In addition, the distribution of demographic variables and risk factors were similar to those in the general population.

The neurodevelopmental theory of psychopathology suggests that exposure to a toxin or event at critical periods of nervous cell development, often the perinatal period, may lead to brain damage and development of different behavioral outcomes. The effects are often subject to dose of exposure, and many mediating and moderating pre and post-natal factors. These behavioral outcomes may be apparent later in development when environmental demands on specific functions are higher or at times of neuronal reorganizations. Multiple developmental pathways and outcomes may result from a single exposure (Cicchetti & Walker, 2013). This work suggests that NSS, which are manifestations of brain damage, are not "soft" at all. NSS are associated with poor cognitive performance in children and with higher risk of ADHD. The underlying mechanisms for these associations are not clearly defined. A shared neurological substrate is one proposed hypothesis, but it does not necessarily suggest a causal link. However, reverse causation is unlikely in any of these associations. While our results do not pinpoint underlying mechanisms for these associations, they suggest that these childhood conditions are rooted in neurodevelopment. NSS, however, were not associated with MDD at any stage of life. While our results maybe challenged by methodological limitations in design and measurement, it is possible that the brain damage manifested by NSS is not significant enough to affect MDD.

However, when MDD occurs, attention and cognition would be affected as part of the depressive syndrome. Another explanation is that NSS and MDD are neurobiologically different.

Future research is needed to replicate these findings and to explore the underlying mechanisms for these associations, neuroimaging, functional neuroimaging and genetic studies may help establish underlying mechanisms. The evidence so far did not fully succeed in localizing NSS or these childhood conditions (Colom et al., 2006; Dazzan et al., 2006; Luders et al., 2009). In addition, prospective designs examining NSS or a proxy of them prior to the age of development of these disorders may prove a temporal association and suggest causation. Long term follow up studies are needed to examine whether these association will persist beyond the age of brain maturation in adolescence and dissipation of NSS; or whether these early negative impacts, will have long term consequences, regardless of the presence of NSS. Of vital importance is research targeting the clinical implications of these findings. Clinical research examining the effectiveness of interventions targeting NSS, such as occupational therapy and training in improving cognitive performance and ADHD is warranted. This is particularly important for ADHD, where such interventions can be offered as adjunct treatment to optimize remission or as an alternative treatment when pharmacotherapy is not desirable.

Chapter 1: Neurological Soft Signs and Cognition in Early Childhood

Neurological Soft Signs and Cognition in Early Childhood

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Abstract

Background: Neurological Soft Signs (NSS), subtle but abnormal motor and sensory signs and involuntary movements, have been implicated as risk factors for poor cognitive performance in small-scale studies. Here we investigate the associations between NSS and multiple domains of cognitive functioning in a large, population-based cohort and evaluate sex differences in these associations.

Methods: We analyzed data from 35,710 seven-year old children in the Collaborative Perinatal Project to study the association between NSS assessed during a neurological exam and cognitive performance using multiple linear regression models adjusting for demographics as well as risk factors for brain injury and aberrant neurodevelopment.

Results: NSS were associated with poor cognitive performance across all domains. The higher the count of signs exhibited by a child, the lower the cognitive score. Each additional soft sign was associated with lower full scale IQ,(b =-4.83, 95% CI = -5.06, -4.60), performance IQ (b = -4.28, CI = -4.54, -4.02), and verbal IQ scores (b = -4.53, CI = -4.76, -4.30); as well as arithmetic (b = -4.06, CI = -4.26, -3.85), spelling (b = -3.53, CI = -3.75, -3.30), and reading (b = -4.00, CI = -4.26,-3.75) scores on the Wide Range Achievement Test (WRAT). Except for the WRAT spelling test (t = -2.14**,** p=0.03), the associations between NSS and cognitive test scores did not differ by sex.

Conclusions: There is an association between NSS and poor cognitive performance that is not attributable to established risk factors for brain injury and aberrant neurodevelopment. Further research should seek the mechanisms for this association and should evaluate the effectiveness of preventive interventions targeting NSS in children.

Introduction

Neurological soft signs (NSS) are clinically detectable abnormalities that include poor motor coordination, sensory perceptual difficulties, and involuntary movements. NSS are thought to be manifestations of a minor non-specific cerebral dysfunction (either localized or diffuse) (Dazzan & Murray, 2002) that could be caused by factors such as brain injury during the perinatal period, aberrant neurodevelopment that is either genetic in origin (Nichols & Chen, 1981) or due to intrauterine exposure to toxins (Ferriero, 2004).

Children with NSS were found to have lower intelligence scores (Obiols et al., 1999; Semerci, 2000) and academic achievement (Biswas, Malhotra, Malhotra, & Gupta, 2007; Schonfeld, Shaffer, & Barmack, 1989) than children without NSS; adolescents with NSS had longer reaction time, interference, and lower accuracy scores on tests of executive functions (Cai et al., 2013). The associations of NSS with cognitive functions are not limited to children and adolescents, but extend throughout the life course, as they have been reported in elderly patients with Mild Cognitive Impairment (Li et al., 2012). Results from imaging-based studies suggest that the association between NSS and cognition may arise partly through shared neural substrates or networks (Cai et al., 2013; Chan, Rao, Chen, Ye, & Zhang, 2006; Rao et al., 2008).

There are two major gaps in the literature regarding the role of NSS in cognitive development: 1) the domain-specificity of the involvement of NSS in cognition, and 2) whether there are sex differences in the association between NSS and cognition.

While prior studies have shown consistent associations of NSS with poor cognitive performance, there is inconsistent evidence as to the specific domains of cognition most strongly associated with NSS. Finding that the association between NSS and cognitive performance is domain-specific could clarify the association by pointing the way to specific neurobiological

mechanisms or brain regions. Other than the influence of NSS on executive functions, specifically the arrows task (AT) and the stroop color-word test (SCWT) (Cai et al., 2013), domain specific effects of NSS have not been investigated. Nevertheless, recent studies have suggested that neural correlates of intelligence, similar to NSS (Dazzan et al., 2006), are likely to be distributed throughout the brain rather than localized to specific areas (Colom et al., 2006; Luders et al., 2009).

With respect to sex differences, NSS are more common and more enduring among boys than girls; this difference could result in part from differential timing of maturation of the brain and to higher rates of delivery and labor complications in boys (Cai et al., 2013; Martins et al., 2008; Shafer et al., 1986). In the current study we have a unique opportunity to investigate sex differences in the association between NSS and cognition adjusting for delivery and labor complications and other potential indicators of brain injury that are often hypothesized to be the reason behind sex differences in NSS. If in fact the adjusted associations between NSS and cognitive test scores differ by sex, this would cast doubt on a conventional explanation for such differences.

In addition to addressing gaps in the literature regarding domain specificity and sex differences in the association between NSS and cognitive performance, the current study extends prior work in two respects related to methodology. First, prior studies included limited adjustment for perinatal factors, which are potentially important confounders in the association between NSS and cognition (Breslau et al., 2000; Buchanan & Heinrichs, 1989; Chen & Chan, 2003; Heikura U, 2008; Koutra, 2012; Nichols & Chen, 1981). Second, prior studies most frequently used dichotomous measures indicating presence or absence of NSS, NSS manifesting above an arbitrary cutoff, measures based on latent variable approaches that have showed

inconsistent results (Malla, Norman, Aguilar, & Cortese, 1997; Schröder et al., 1991), or functional categorizations of NSS that do not necessarily reflect underlying mechanisms (Breslau et al., 2000; Cai et al., 2013; Shafer et al., 1986; Shaffer, 1978). Functional categorizations are often based on presumed neuro-anatomical substrate, which is debatable in the absence of defined focal lesions (Sanders & Keshavan, 1998). Accordingly, we use a quantitative measure of NSS, which we suggest is more reflective of the nature of the underlying brain dysfunction and it captures the severity of NSS. We use data from the Collaborative Perinatal Project (CPP), a landmark United States pregnancy cohort with comprehensive assessments of children's neurologic and cognitive functioning to investigate the relation between NSS and cognition.

Methods

Study population

The CPP is a national multi-site prospective cohort study that recruited 48,197 pregnant women at 12 university-affiliated medical centers between 1959 and 1966. The CPP followed women and their offspring through pregnancy, delivery, and the first 7 years of the children's life (Broman, 1984b; Niswander & Gordon, 1972). The aims of the CPP included identifying the developmental consequences of pregnancy and delivery complications. Out of the 41,911 children who underwent neurological examination at age 7, the analysis sample for this study included offspring with complete data on all study variables (n=35,710).

Measures

NSS were measured during a neurological examination done according to the CPP protocol. Board certified pediatricians performed the exam, blinded to the child's medical record, under the supervision of a senior board certified pediatric neurologist. The CPP exam assessed 3

functional subgroups of NSS: abnormalities in motor coordination, sensory functions, and involuntary movements.

Motor coordination signs consisted of the following items: dysdiadochokinesia, dysmetria, ataxia, and awkwardness. Dysdiadochokinesia is the difficulty in performing rapid alternating movement of the hands and feet in a smooth and fluent way. Dysmetria is the difficulty in accurately positioning a limb, especially in the terminal part during movement. Ataxia is the failure to synthesize component muscular actions into a smooth and accurate movement. These signs were elicited by asking participants to perform the following tests: rapid alternating movement, finger to nose, heel to knee with eyes open and closed, finger pursuit, rapid individual finger movement, and complex activities like fastening buttons or zippers, tying shoes, writing, or picking up small objects.

Sensory neurological soft signs consisted of: right and left identification, astereognosis, and position sense. A child was asked to perform these tests with emphasis on the right or left hand, and their initial response was recorded. Astereognosis, which is the inability to identify three-dimensional object by touch without visual input, was tested by placing visually recognizable objects one at a time into the child's hand and asking him/her to identify them with their eyes closed. Position sense was performed using two tests: 1) passive movement of the great toe, where the examiner grasps the big toe by the sides and passively moves it through a small arc. The child is then asked to give the direction of the movement during the motion on at least five trials. 2) Location of a finger in space, where the examiner places one of the child's index fingers in space and then, with the child's eyes closed, asks them to touch it with his/her other index finger.

Involuntary movement consisted of mirror movement and tremors. Mirror movement is involuntary movement in the hand opposite the hand engaged in a simple task. Children were asked to do rapid thumb-forefinger apposition in one hand while the examiner observed the other hand to detect mirror movement. This was repeated for the other hand. Tremors were identified as spontaneous tremors, which are tremors present at rest, and also tremors associated with maintenance of posture.

The CPP neurological examination is substantially similar to the type currently used in research (Buchanan & Heinrichs, 1989; Chen et al., 1995; Convit, Volavka, Czobor, de Asis, & Evangelista, 1994; Denckla, 1985; Jahn et al., 2006; Krebs, Gut-Fayand, Bourdel, Dischamp, & Olie, 2000; Vreeling, Jolles, Verhey, & Houx, 1993). The specific abnormalities counted in our measure of NSS have considerable overlap with abnormalities assessed in modern batteries, namely the Cambridge Neurological Inventory (Chen et al., 1995) and the Krebs (Krebs et al., 2000). The Neurological Evaluation Scale (Buchanan & Heinrichs, 1989), for example, included extra-pyramidal signs and reflexes that are often not defined as soft signs, or signs that are commonly detected in psychotic patients rather than in the general population limiting its use in population studies. Compared to the Brief Motor Scale (Jahn et al., 2006), which only includes items of motor coordination, our measure included sensory and involuntary movement items (see Supplemental Table 1.4 for a review of measures of NSS). The measure of NSS used here was a count of 0, 1, 2, or 3 soft signs (capped at 3 given the small number of children that exhibited 4, 5 or 6 signs (n=55)).

Cognitive performance. Full scale Intelligence Quotient [FSIQ] was assessed using the Wechsler Intelligence Scale for Children (Wechsler, 1949), which contained 7 subtests that evaluate different areas of cognition including verbal (VIQ) and performance intelligence (PIQ).

In addition, the reading, spelling and arithmetic portions of Wide Range Achievement Test [WRAT], which have high validity and reliability (Jastak, 1965), were also analyzed.

Other covariates. We adjusted for variables that could be potential confounders including low birth weight defined as birth weight less than 2.5 Kg (Breslau et al., 2000), socioeconomic status (SES) (Chin-Lun Hung et al., 2015; Heikura et al., 2008; Koutra, 2012) race, sex, risk factors for brain injury or aberrant neurodevelopment, and CPP study site. Family SES at age seven was a weighted percentile of each head of household's education, occupation, and income relative to the US population (Myrianthopoulos & French, 1968). SES scores were divided into 3 categories corresponding to low (0-33% of the distribution), medium (34%-66%) and high (>66%) SES.

History of pregnancy or delivery complications, low Apgar scores, fetal resuscitation after birth, and ICU admission were considered potential confounders as well, as they are potential causes of brain injury due to ischemic, or traumatic processes (Leviton & Nelson, 1992; Nelson & Leviton, 1991). In addition, we adjusted for maternal history of psychiatric or neurologic disorders, maternal smoking, and exposure to prescription drugs during pregnancy, which are risk factors for aberrant neurodevelopment.

Statistical analysis

Three linear regression models were fitted to examine the associations between NSS and the five cognitive test scores. In model 1, we adjusted for demographic factors and birth weight. In model 2, we added pregnancy or labor complications, low Apgar scores at 1 and 5 minutes, fetal resuscitation, and any ICU admission after birth. In model 3, we added maternal history of psychiatric or neurologic disorders, maternal smoking, and exposure to prescription drugs during pregnancy. Using this sequential approach in adjusting for these groups of variables will help us

determine how much of the association is potentially attributable to risk factors for brain injury vs. those for aberrant development.

To investigate specificity of the effect of NSS on cognitive domains, a multivariate multiple regression (Afifi, 2012; Dattalo, 2013) was performed. We tested the hypothesis that the coefficients for NSS are the same for the dependent variables VIQ and PIQ. Similarly, we tested the hypothesis that the coefficients for NSS are the same in the following pairs of dependent variables arithmetic and spelling; arithmetic and reading; and finally spelling and reading domains of the WRAT,

To test for sex differences in the NSS associations, we added an interaction term between sex and NSS to each of the models. To examine if the association between NSS and cognitive tests is due to co-morbid hard signs or localized cerebral disease, a sensitivity analysis excluding those with severe cerebral disease was performed using model 3. Results of the regression analyses are reported in terms of the regression coefficient for NSS and 95% confidence interval (CI). Variance estimates were adjusted for the presence of sibling sets in the analysis sample using generalized estimating equations (GEE).

Results

This study sample included 35,710 children (85% of all CPP children who participated in the age seven assessment). There were 18,022 (50.47%) males and 17,688 (49.53%) females. 9.90% of participants had a birth weight below 2.5 Kg and 37.70% had been exposed to pregnancy or delivery complication. Of the newborn offspring, 7.65% had an ICU admission and 6.00% had resuscitation at birth. There were 16.10% who had a maternal history of neurologic or psychiatric disorder, 4.81% had mothers who used prescription drugs during pregnancy, and 50.12% had mothers who smoked during pregnancy (Table 1.1).

Table 1. 1 Characteristics of children at age 7 in the Collaborative Perinatal Project (n = 35,710)

	Number [%]
Sex	
Males	18,022 [50.47]
Females	17,688 [49.53]
Birth weight	
≥ 2.5 Kg	32,174 [90.10]
< 2.5 Kg	3,536 [9.90]
SES	
High	8,659 [24.25]
Medium	18,054 [50.56]
Low	8,997 [25.19]
Race/Ethnicity	
White	16.963 [47.50]
Black	17,385 [48.68]
Hispanic	1,105 [3.09]
Other	257 [0.72]
Any pregnancy and delivery complications	13,462 [37.70]
Weeks of gestation < 37 weeks	2020 [9.27]
Apgar score at 1 min < 7	8,041 [22.52]

Apgar at 5 min < 7	3017 [8.45]
Resuscitation at birth	2141 [6.00]
ICU admission	2700 [7.56]
Maternal history of neurologic or psychiatric disorders	5749 [16.10]
Exposure to drugs during pregnancy	1,719 [4.81]
Maternal smoking	17,898 [50.12]

The prevalence of any NSS was 31.65% and the total number of NSS signs exhibited by a child ranged from 0 to 6 (Table 1.2). Boys had higher counts of NSS than girls and, in general, had a higher prevalence of the individual signs (Supplemental Table 1.5).

Table 1. 2 Distribution of neurological soft signs at age 7 in the Collaborative Perinatal Project by sex (n = 35,710)

NSS Count	Males	Females	Total
	Number [%]	Number [%]	
0	11,811 [48.39]	12,595 [51.61]	24,406
1	5442 [54.05]	4627 [45.95]	10,069
2	624 [62.40]	376 [37.60]	1000
3	116 [62.37]	70 [37.63]	186
4	24 [58.54]	17 [41.46]	41
5	3 [50.00]	3 [50.00]	6
6	2 [100.0]	0 [0.00]	2

The distributions of cognitive test scores according to the number of NSS are shown in Figures 1.1 (Wechsler tests) and 1.2 (Wide Range Achievement Tests, WRAT). The mean FSIQ, its performance, and verbal domains, and the means of the arithmetic, spelling, and reading domains of the WRAT were lower in children with more NSS. In fact, there was approximately a standard deviation difference in cognitive test scores between children with 0 vs. 3 or more NSS. Boys had somewhat similar mean cognitive tests' scores as girls (Supplemental Figures 1.3,4).

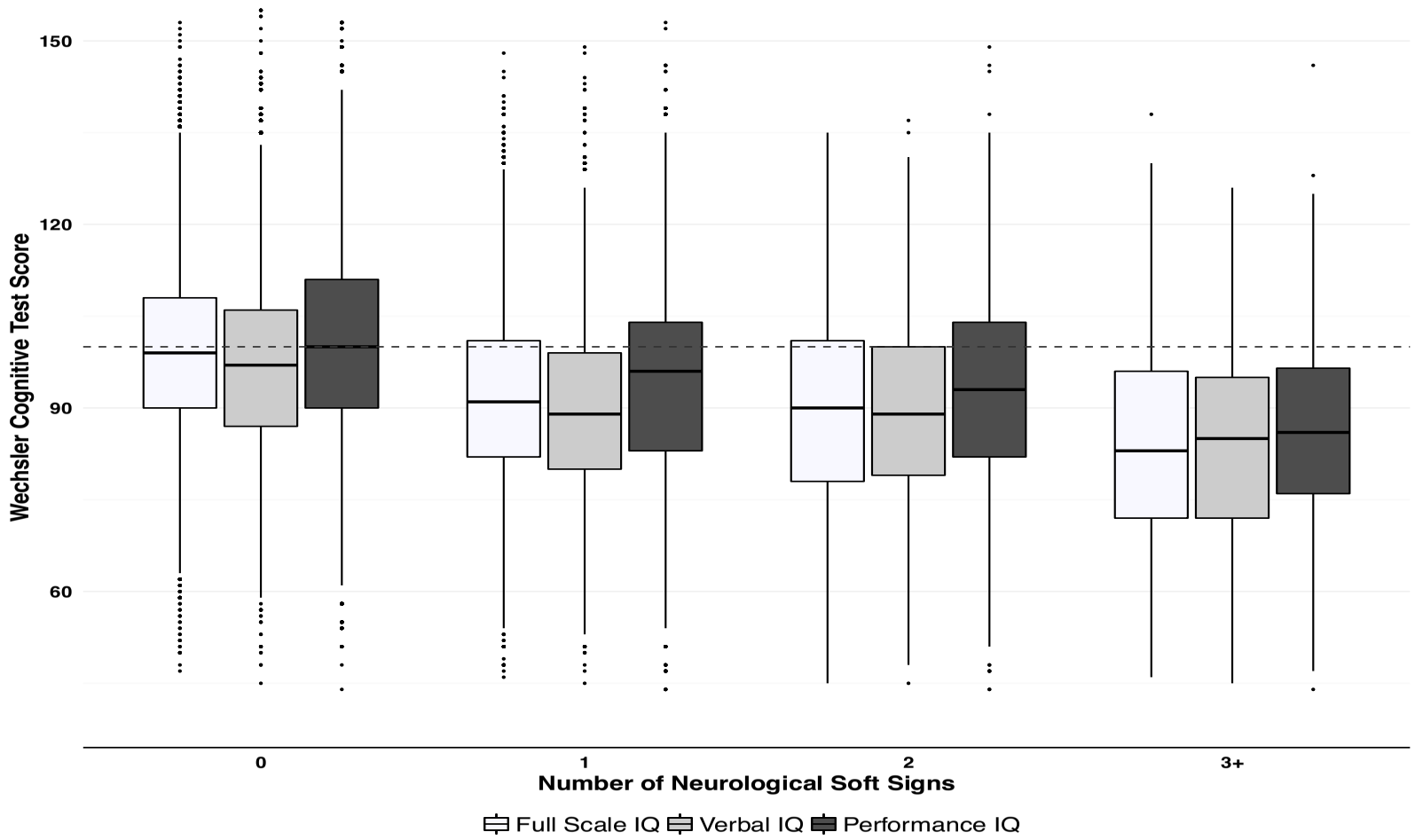


Figure 1.1 Mean Wechsler test scores according to the number of neurological soft signs in children at age 7 in the Collaborative Perinatal Project (n= 35,710)

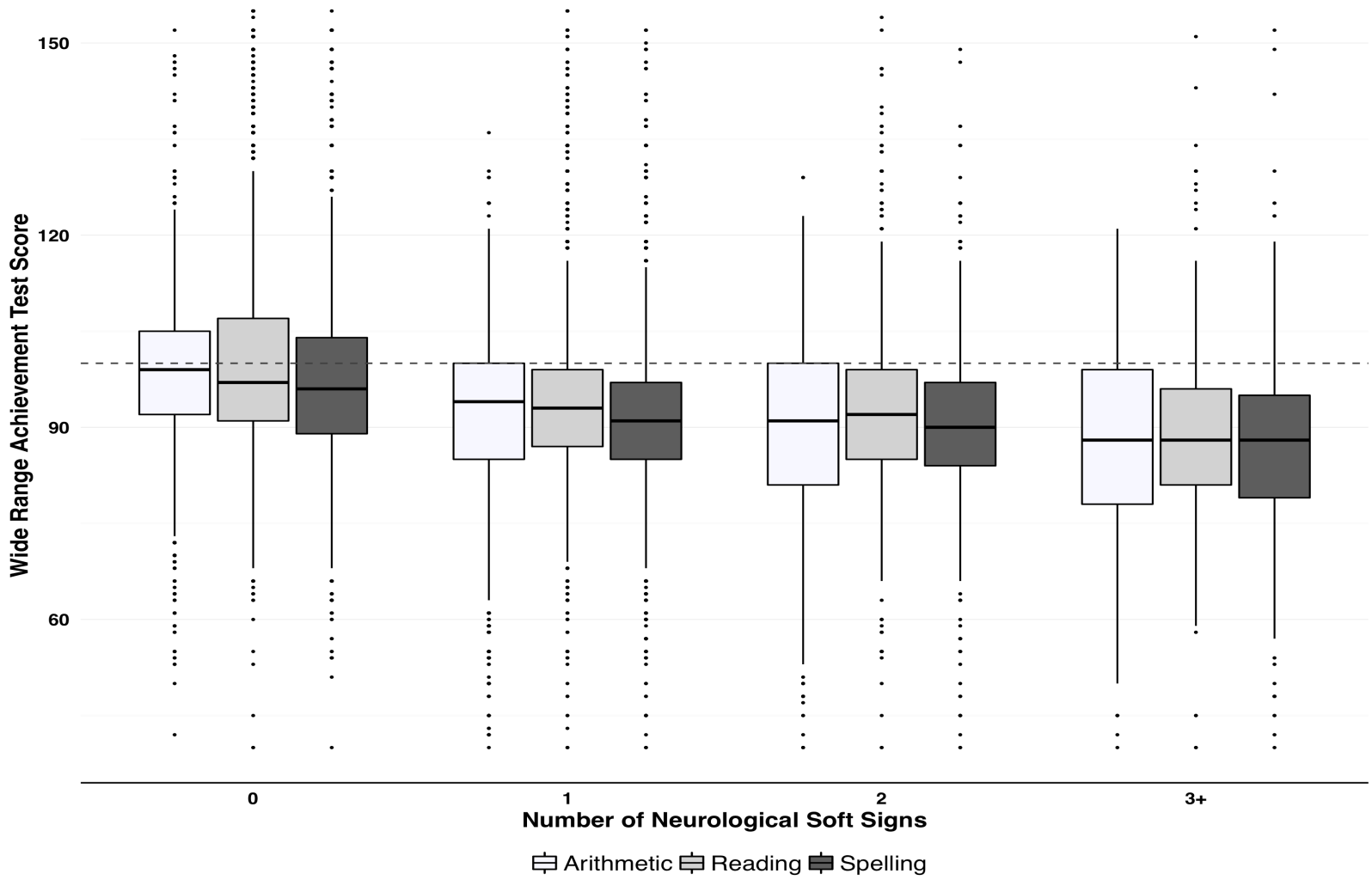


Figure 1.2 Mean Wide Range Achievement Test (WRAT) scores according to the number of neurological soft signs in children at age 7 in the collaborative perinatal project (n= 35,710)

The results of linear regression analyses of children's cognitive test scores are shown in table 1.3. When adjusting for child age, race, sex, SES, birth weight, and study site (Model 1), the number of NSS observed was inversely associated with FSIQ total score (b [linear regression coefficient] = -4.83, CI = [-5.07, -4.60]), PIQ (b = -4.28, CI = [-4.54, -4.02]), and VIQ (b = -4.53, CI = [-4.76, -4.50]), as well as with WRAT scores on arithmetic (b = -4.07, CI = [-4.27, -3.86]), spelling (b = -3.53, CI = [-3.75, -3.30]), and reading (b = -4.00, CI = [-4.26, -3.75]). Thus, for each additional soft sign observed during the clinical examination, a child's expected IQ score was approximately 4 points lower. In Models 2 and 3, which adjust sequentially for a wider range of potential confounders, the regression coefficients for the association between NSS and cognitive test scores were not meaningfully changed.

Table 1. 3 Linear regression models of cognitive tests' scores at age 7 in the Collaborative Perinatal Project (n = 35,710)

Cognitive tests	Model 1: Demographics only	Model 2: Demographics, pregnancy and delivery complications	Model 3: Demographics, pregnancy and delivery complications and developmental risk factors
Dependent variables	Regression Coefficient [95% CI] NSS	Regression Coefficient [95% CI] NSS	Regression Coefficient [95% CI] NSS
FSIQ	-4.83 [-5.07, -4.60]*	-4.83 [-5.07, -4.60]*	-4.83 [-5.07, -4.60]*
Performance	-4.28 [-4.54, -4.02]*	-4.28 [-4.54, -4.02]*	-4.28 [-4.54, -4.02]*
Verbal	-4.53 [-4.76, -4.50]*	-4.53 [-4.76, -4.30]*	-4.53 [-4.76, -4.30]*
WRAT			
Arithmetic	-4.07 [-4.27, -3.86]*	-4.06 [-4.27, -3.85]*	-4.06 [-4.26, -3.85]*
Spelling	-3.53 [-3.75, -3.3]*	-3.53 [-3.75, -3.31]*	-3.53 [-3.75, -3.30]*
Reading	-4.00 [-4.26, -3.75]*	-4.00 [-4.26, -3.75]*	-4.00 [-4.26, -3.75]*

Note. * p<.001;

Model 1: controlled for child age, race, sex, SES, birth weight, study site.

Model 2: controlled for child age, race, sex, SES, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, and ICU admission.

Model 3: controlled for child age, race, sex, SES, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, ICU admission, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy.

Children with NSS had lower scores on VIQ compared to PIQ ($F_{(1)} = 4.06$,, P = 0.043). The additional decrease in VIQ per sign (0.25) is 0.02 of the standard deviation (SD) unit of 15. Among the WRAT scores, children with NSS had lower scores on the reading and arithmetic compared to spelling ($F_{(1)} = 51.7$, P = 0.0001; $F_{(1)} = 41.35$, P = 0.0001 respectively). The additional decrease in the reading score per sign (0.47) is 0.03 of the SD and that for arithmetic (0.55) is 0.04 of the SD. However, there was no significant difference in the effect of NSS on arithmetic compared to reading ($F_{(1)} = 0.48$,, P = 0.49).

In comparing the association of NSS with cognitive test scores between boys and girls, girls had steeper rates of decline than boys, but the interaction terms between sex and NSS were not statistically significant except for spelling. For the spelling test, girls had a steeper rate of decline (b= -4.01, [CI = -4.26, -3.36]) than boys (b= -3.53, [CI= -3.75, -3.30]), (b for the interaction = -0.48 ,p = 0.03); however, this significant interaction would not survive correction for multiple testing.

Finally, the results of sensitivity analysis excluding 449 children with severe cerebral disease were similar to the results derived from the full sample (Supplemental Table 1.6).

Discussion

In this study, seven-year old children with NSS had lower scores on tests of cognitive performance, by approximately 4 points (about 1/3 of a standard deviation) for each soft sign observed. These results suggest that NSS are not “soft” at all and are not merely signs of neuronal immaturity (Camp et al., 1978; Foster & Margolin, 1978; Hall & Kramer, 1995), but rather they have a clinically meaningful association with cognitive development.

Our findings replicated previous studies in which children with NSS were found to have lower IQ scores (Breslau et al., 2000; Obiols et al., 1999; Semerci, 2000) than children without

NSS. Most prior studies were small or analyzed qualitative or dichotomous measures of NSS. This is the first large-scale study of the association between the count of NSS and multiple domains of cognitive performance.

Our results were similar to findings by Breslau and colleagues who found that children with NSS had a 2 to 4 fold increase in the risk of having an IQ less than 85 (Breslau et al., 2000). NSS were associated with all domains of cognitive tests and all regression coefficients were within 1 point of each other. However, we found a more pronounced effect on VIQ compared to PIQ (0.02 of SD) and the reading and arithmetic domains compared to spelling (0.04 of SD and 0.03 of SD respectively). These results should be interpreted with caution, considering the small differences between these sub-domains and in light of evidence suggesting that neuronal correlates for NSS and intelligence are distributed throughout the brain (Colom et al., 2006; Dazzan et al., 2006; Luders et al., 2009). However, if this specific effect is true, this will further help in localizing NSS and understanding their etiology.

The association between NSS and cognitive performance was independent of established risk factors for brain injury and aberrant neurodevelopment. This potentially argues for preventive interventions such as occupational therapy and training that target NSS in order to improve cognitive outcomes.

In our study, similar to other studies (Cai et al., 2013; Shaffer, 1978), the prevalence of NSS was higher in males compared to females. In general, however, boys and girls had similar scores on all cognitive tests, and our findings were consistent with prior studies on sex differences in cognitive performance (Halpern, 1997; Hedges & Nowell, 1995). Our sample consisted of children at age 7, which is prior to the age of brain maturation. Therefore, sex differences in the count of NSS cannot be fully explained by the differential age of maturation

between boys and girls. However, the association between NSS and cognitive performance was largely similar for boys and girls, irrespective of adjustment for labor and delivery complications that are often hypothesized to explain these sex differences. There was an indication of a more pronounced association between NSS and spelling scores among girls, but given the number of sex differences examined here this result requires replication.

Of note, the association between NSS and cognition was tested prior to the age when neuronal maturation occurs in adolescence. This raises questions about whether the association with cognitive outcomes would persist after brain maturation and potential resolution of some, if not all, of these signs. In particular, would the cognitive deficits persist only among those who continue to exhibit soft signs beyond childhood? Furthermore, if the deficits do not persist, could these children overcome childhood cognitive deficits and draw near their peers? Or whether these early deficits in such a critical learning period will irremediably impact their developmental trajectory. The answers to all of these questions require studies that follow children into adulthood.

Limitations

Although the CPP used a prospective cohort design and factors suggestive of brain injury were collected prior to age 7, both NSS and cognitive performance were assessed concurrently at 7 years. Accordingly, temporality of the association between NSS and cognitive performance could not be resolved; however, mechanisms for reverse causation are not biologically plausible, as it is unlikely that poor cognitive performance would cause NSS.

Other limitations of this study include potential errors in measuring NSS, although our measure is not different from modern batteries. The same applies for measuring cognitive

performance; we did not test for a comprehensive list of cognitive tests but we chose those that are considered significant parts of any contemporary cognitive test.

As with other prospective cohort studies, our study could have been biased due to attrition. However, children lost to follow-up before age 7 did not differ on several demographic and neonatal characteristics from the children who were examined (Broman, 1984a). Similarly, children followed until age 7 were found to be representative of all CPP offspring (Nichols & Chen, 1981).

Conclusion

Children with NSS had lower scores on tests of cognitive performance independent of risk factors for brain injury and aberrant neurodevelopment. Future work, therefore, should examine the effectiveness of preventive interventions specifically targeting NSS (Blank, Smits-Engelsman, Polatajko, & Wilson, 2012) as risk factors for poor cognitive performance. Further work is also needed to understand the underlying mechanisms and the possible persistence of cognitive deficits among children with NSS into and beyond adolescence. We expect that in the absence of interventions it will be difficult to compensate for childhood cognitive deficits resulting in life long impairment irrespective of the resolution of NSS. Regarding the sex differences, future work should follow up on the question of sex differences in NSS (which are elevated among boys) and in the consequences of NSS (which were largely similar between boys and girls in our analyses).

Finally, a potential clinical implication of our study is that NSS are easily detected during annual physical exams, and could therefore be incorporated into a relatively inexpensive screening for problems in cognitive development. Children thus identified could be targeted for

treatment interventions such as occupational and physical therapy if the effectiveness of such interventions can be established.

Supplemental Material

Supplemental Table 1. 4 Neurological soft signs scales comparisons

	Brief Motor Scale (BMS)	The Cambridge Neurological Inventory	The Neurological Evaluation Scale	Krebs	NCPP (18 signs)	Our study
Items						
Motor	Dysdiadochokinesia Oseretsky Foot tapping Bilateral rhythm tapping Gaze impersistence (coordination) Pronation-supination	Finger-thumb tapping (L, R) Finger-thumb opposition (L, R) Dysdiadochokinesia (L, R) First-edge-palm test (L,R) Oseretsky test (L,R)	Tandem walk Rapid alternating movement (L,R) Finger-thumb opposition (L,R) Finger –nose test (L,R) (coordination) First-ring (R,L) First-edge-palm (L,R) Oseretsky Rhythm tapping	Hand dysrhythmia Fist-edge-palm Foot dysrhythmia Alternative movement: foot speed Alternative movement :hand speed Standing heel to toe	Dysdiadochokinesia Dysmetria Ataxia Awkwardness Other	Dysdiadochokinesia Dysmetria Ataxia (rapid alternating movement, finger to nose, heel to knee with eyes open and closed, finger pursuit, rapid individual finger movement and complex activities

	Finger-thumb-opposition Fist-ring Fist-edge-palm Rhythm production (motor sequencing)		(sequencing)	(coordination) Romberg Apraxia Tandem walk Finger to nose Gait Tongue protrusion (integration)		like doing buttons or zippers, tying the shoes, writing, or picking up small objects)
Sensory		Extinction Finger agnosia (L,R) astereognosis (L,R) Figureesthesia (L,R) Left-right orientation	A-V integration astereognosis (L,R) Figureesthesia (L,R) Extinction L/R confusion	astereognosis Hand-face Constructive apraxia Figureesthesia Right/left recognition Right/left confusion	Location of finger in space astereognosis fine astereognosis gross	astereognosis R-left identification Position sense

				Lateral preference Right/left asymmetry		
Involuntary movements		Mirror Movement 1 (during finger thumb opposition) 2 (during Dysdiadochokinesia (L,R) Go/no-go test	Adventitious overflow (L,R) Romberg test Tremor (L,R) Mirror movement Synkinesis Convergence (L,R) Gaze impersistence (L,R) Glabellar reflex Snout reflex Grasp reflex Suck reflex	Mirror movement Abnormal movement and posture	Fasciculations Myoclonus Spontaneous tremors Intention tremors Athetosis Chorea Dystonia Ballismus Tic Mirror movement Other abnormal movement	Mirror movement Tremor
Notes on coding	0,1,2	0,1,2	0,1,2		0,1	0,1
Notes on	Sum	Sum of each subscale over max			Sum,	Sum

scoring		total			2 or more
	A measure of only motor symptoms		Not a direct measure of NSS, but of the most common signs found in psychotic patients		
Reference	(Jahn et al., 2006)	(Chen et al., 1995)	(Buchanan & Heinrichs, 1989)	(Krebs et al., 2000)	(Shaffer et al., 1985)

Supplemental Table 1. 5 Distribution of individual neurological soft signs at age 7 in the collaborative perinatal project overall and by sex (n=35,710)

NSS	Males	Females	Total
	Number [%]	Number [%]	Number [%]
Motor			
Ataxia	78 [0.22]	36 [0.10]	114 [0.32]
Awkwardness	4 [0.01]	5 [0.01]	9 [0.03]
Dysdiadochokinesia	632 [1.77]	355 [0.99]	987 [2.76]
Dysmetria	140 [0.39]	79 [0.22]	219 [0.61]
Sensory			
Astereognosis	176 [0.49]	164 [0.46]	340 [0.95]
Left_right identification	5269 [14.75]	4393 [12.30]	9662 [27.06]
Position sense	326 [0.91]	276 [0.77]	602 [1.69]
Involuntary Movement			
Mirror movement	438 [1.23]	313 [0.88]	751 [2.10]
Tremor	98 [0.27]	51 [0.14]	149 [0.42]

Supplemental Table 1. 6 A comparison between the original sample and the complete case analysis sample in key demographics and exposure distribution

	Sample: all children with neurological exam at age seven (n = 41,911) Prevalence %	Sample: children with complete data (n= 35,710) Prevalence %
Female	49. 45	49.53
Male	50.55	50.47
Birth weight < 2.5 Kg	9.31	9.90
SES		
High	23.46	24.25
Medium	49.24	50.56
Low	24.78	25.19
Prevalence of one or more NSS	32.06	31.65
Motor		
Ataxia	0.33	0.32
Dysdiadochokinesia	2.81	2.76
Dysmetria	0.64	0.61
Awkwardness	0.04	0.03
Sensory		
Astereognosis	1.05	0.95

R-L identification	25.96	27.06
Involuntary movement		
Mirror movement	2.14	2.10
Tremor	0.42	0.42

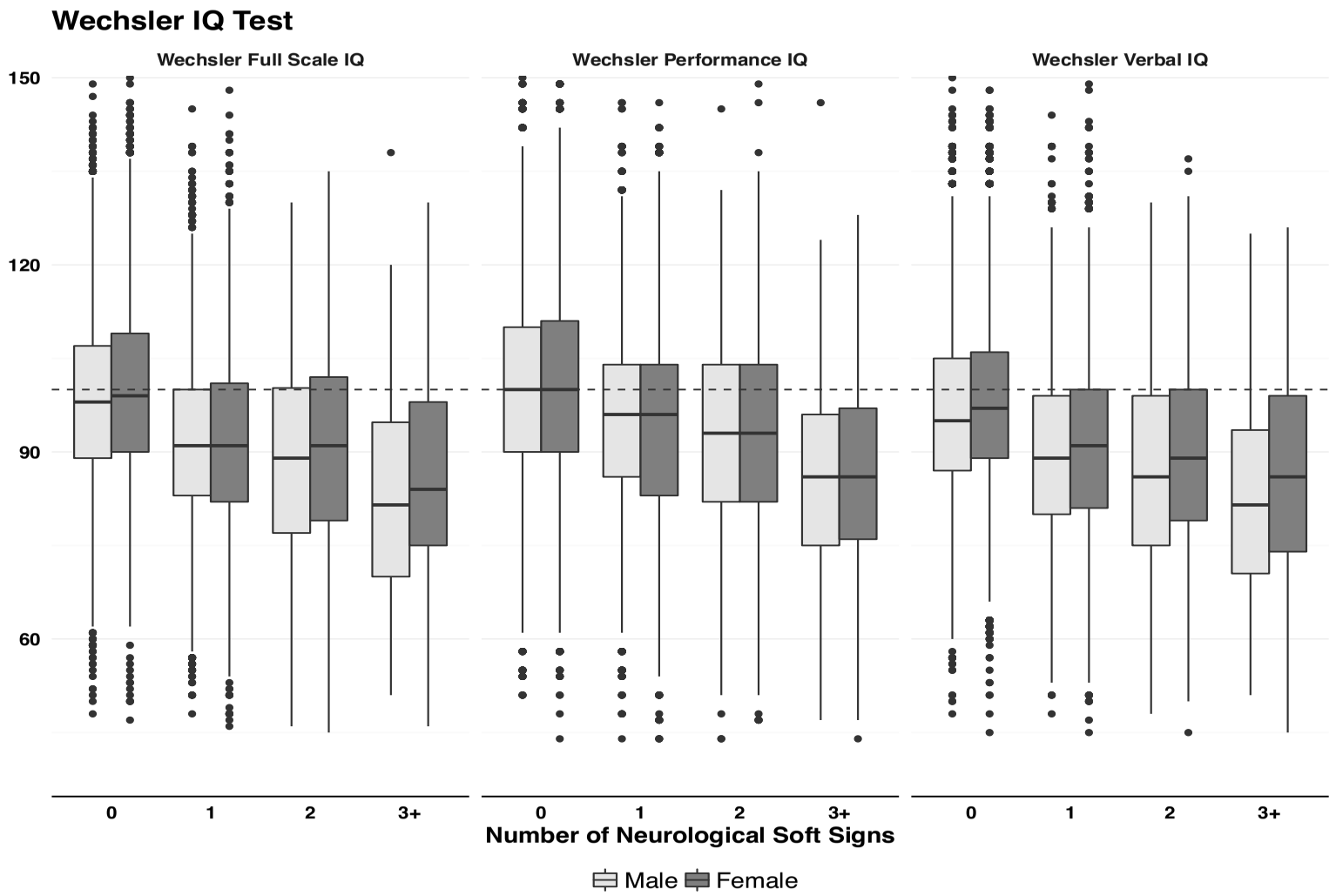
Supplemental Table 1. 7 Linear regression models predicting cognitive tests' scores by count of neurological soft signs at age 7 in the collaborative perinatal project, comparing the full sample to the sample excluding children with severe cerebral disease.

Cognitive tests	Model 3: Demographics, pregnancy and delivery complications and developmental risk factors (n = 35,710)	Model 3: Demographics, pregnancy and delivery complications and developmental risk factors after excluding children with severe cerebral disease (n = 32,830)
	Regression Coefficient [95% CI]	Regression Coefficient [95% CI]
Dependent variables	NSS	NSS
FSIQ	-4.83 [-5.07, -4.60]*	-6.62 [-6.95,-6.28]*
Performance	-4.28 [-4.54, -4.02]*	-3.03 [-3.22, -2.83]*
Verbal	-4.53 [-4.76, -4.30]*	-3.59 [-3.78, -3.40]*
WRAT		
Arithmetic	-4.06 [-4.26, -3.85]*	-4.05 [-4.27, -3.84]*

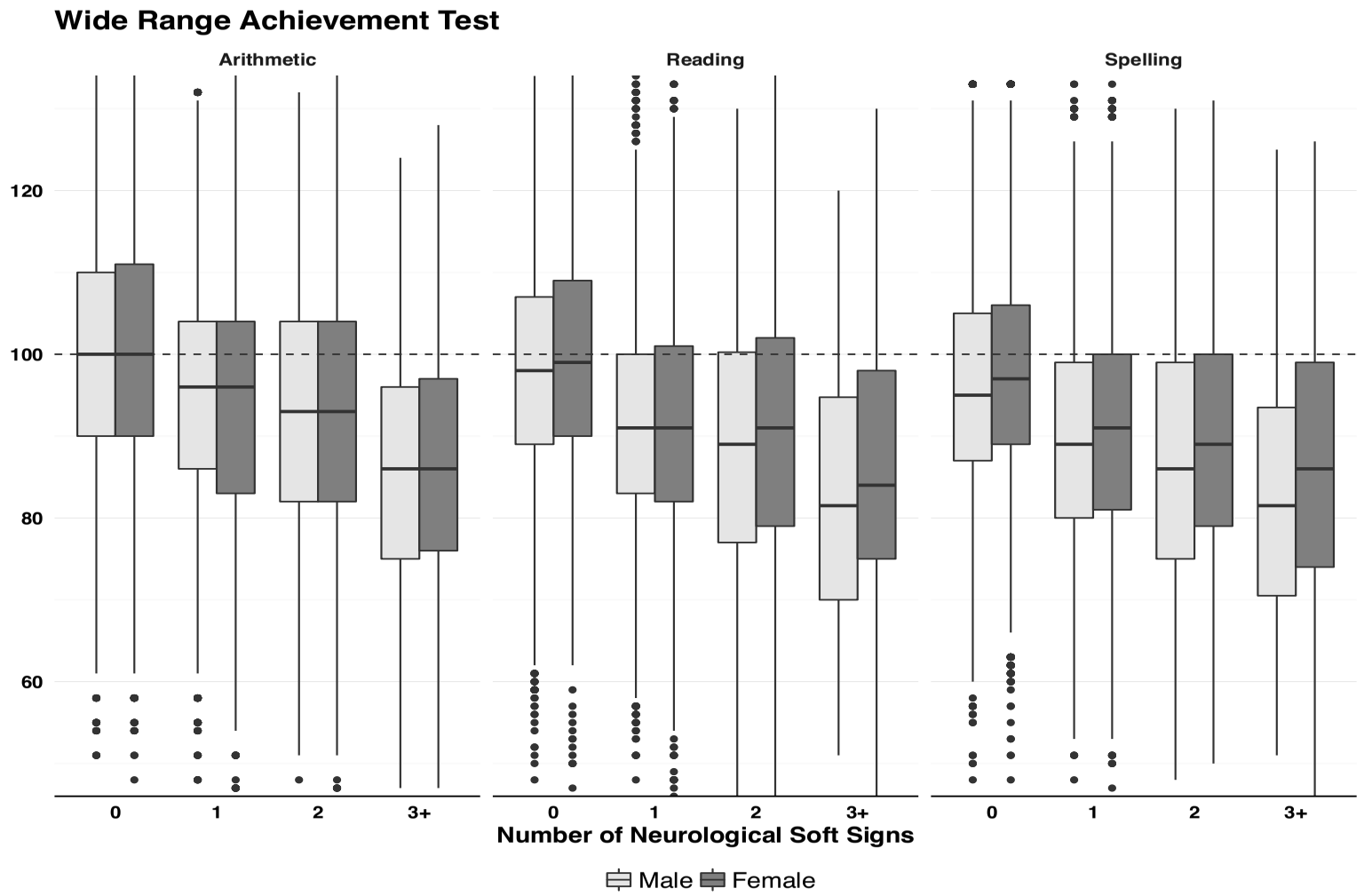
Spelling	-3.53 [-3.75, -3.30]*	-3.47 [-3.70, -3.24]*
Reading	-4.00 [-4.26, -3.75]*	-3.94 [-4.20,-3.67]*

Note. *p <.001;

Controlled for child age, race, sex, SES, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, ICU admission, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy



Supplemental Figure 1. 3 Mean Wechsler test scores according to the number of neurological soft signs by sex in children at age 7 in the collaborative perinatal project (n= 35,710)



Supplemental Figure 1. 4 Mean Wide Range Achievement Test (WRAT) scores according to the number of neurological soft signs by sex in children at age 7 in the collaborative perinatal project (n=35,710)

Chapter 2: Neurological Soft Signs and Attention Deficit Hyperactivity Disorder and Its Subtypes

Neurological Soft Signs and Attention Deficit Hyperactivity Disorder and Its Subtypes

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Abstract

Background: It is known that neurological soft signs (NSS) are more prevalent in children with Attention Deficit Hyperactivity Disorder (ADHD). However, this is the first study to investigate the association using a longitudinal design in a community sample. Further, it examines the association between NSS and the different subtypes of ADHD, specifically the hyperactive subtype considering the hypothesized underlying neuropathology.

Methods: We analyzed data from 2,048 participants from the New England Family Study (NEFS), that followed the adult offspring of the Boston and Providence sites of the Collaborative Perinatal Project [CPP], to study the association between NSS, a selected group of motor and sensory signs and involuntary movement measured during a neurological exam at age 7, and lifetime diagnosis of ADHD and its subtypes. We used multiple logistic regression models, and adjusted for demographic variables and risk factors for brain injury and aberrant neurodevelopment.

Results: NSS increased the odds of lifetime ADHD diagnosis by 70% (OR= 1.7, 95% CI=1.4,2.2). Specifically, NSS increased the odds of the combined subtype by 80% (OR= 1.8, CI= 1.3,2.6), followed by the hyperactive subtype (OR=1.6, CI= 1.2, 2.2), and last the inattentive subtype (OR= 1.5, CI= 1.2,2.2). However, the association lacked specificity for subtypes.

Conclusions: Our results suggest that NSS is associated with increased risk for ADHD and therefore future work should explore the benefits of incorporating NSS in the clinical evaluation and treatment of ADHD.

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a neuro-developmental disorder that affects approximately 5.3% of school-aged children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007); prevalence rates often range from 4 to 12%, depending on type of sample (Brown et al., 2001; Faraone, 2003). Children with ADHD often underperform and a significant number of them require special services, adding to the already high economic burden of the disorder (Barkley, 2016). It is associated with cognitive deficits, psychiatric comorbidities, low self-esteem and high risk for substance abuse and criminality in adolescence and adulthood (Barkley, Fischer, Smallish, & Fletcher, 2004; Satterfield et al., 2007).

Neurological soft signs (NSS) are neurological abnormalities that are thought to be manifestations of a minor non-specific cerebral dysfunction that could be either localized or diffuse (Dazzan & Murray, 2002). They include poor motor coordination, sensory perceptual difficulties, and involuntary movements. The minor cerebral dysfunction, manifested by NSS, is often hypothesized to be due to factors such as brain injury that occurred perinatally, or an aberrant neurodevelopment that is genetic in origin (Nichols & Chen, 1981), or intrauterine exposure to toxins (Ferriero, 2004).

Prior research suggested a link between NSS and ADHD. The evidence for such a link was based on the following findings: 1) A higher rate of NSS in children with ADHD; based on clinical samples (Cardo et al., 2008; Patankar et al., 2012; Uslu et al., 2007). 2) A longitudinal study that followed children with "Deficits in Attention and Motor Control and Perception" (DAMP) in Sweden found that NSS were associated with severe variants of ADHD (Gillberg, 2003). 3) NSS improve with psychostimulants, the first line treatment for ADHD, although the

improvement in NSS did not correlate with the improvement in ADHD (Hrtanek et al., 2015; Lerer & Lerer, 1976; Lerer, Lerer, & Artner, 1977).

The higher prevalence of NSS in children with ADHD is hypothesized to be due to shared neural regions or networks, specifically the prefrontal cortex. It is hypothesized that alteration in the neural networks for motor control inhibition is at the base of the pathophysiology of NSS in children with ADHD, as well as a possible central role of dopamine in these neural circuits (Pasini & D'Agati, 2009). Thus, this may suggest a stronger association between NSS and the hyperactive-subtype ADHD.

In this study, we revisit the association between NSS and ADHD, by examining whether NSS are associated with higher rate of ADHD but in a community sample rather than a clinical sample. Furthermore, we examine if NSS specifically predict the risk of hyperactive subtype vs. other subtypes.

To answer these questions, we used data collected from two studies of the New England Family follow up studies (NEFS) of the Collaborative Perinatal Project (CPP), a prospective cohort, controlling for important confounding factors such as perinatal factors.

In addition to addressing the above questions on the association between NSS and ADHD and its specificity, the results of this analysis may provide some insight on the predictive value of NSS that could be potentially targeted by preventive strategies or open an avenue for an alternative or supplementary therapeutic options for ADHD.

Methods

Study Population

Our sample includes participants from two studies of the NEFS project, a series of follow up studies that followed the adult offspring of the CPP. The CPP started as a multi site prospective cohort study that recruited 48,197 pregnant women at 12 university-affiliated medical centers between 1959 and 1966. The CPP followed women through pregnancy and delivery and their offspring for the first 7 years of life (Broman, 1984b; Niswander & Gordon, 1972). The NEFS was established to locate and interview the adult CPP offspring at the Providence, Rhode Island and Boston, Massachusetts's sites (Gilman et al., 2008). Selection of the participants for the 5 component studies of the NEFS occurred over multiple phases, a stratified random sample was drawn from the entire cohort for each of the follow up studies. Only two of the studies included structured diagnostic interviews for ADHD, the Learning Disabilities study (LD), and Transdisciplinary Tobacco Use Research Center (TTURC) phase 1 and 2 studies. Between 1995-1999, 452 subjects with learning disabilities and a random sample of 610 control participants were selected to study the typologies and determinants of learning disabilities; of those 720 completed the interviews and became part of the LD study (Buka, Tsuang, & Lipsitt, 1993). Between 1999-2009, a multi-stage sampling procedure was done to select 2271 eligible participants based on smoking status and educational attainment. 1625 completed interviews to be part of the TTURC study. The objective of this study was to identify determinants of smoking, its life course and response to treatment (Gilman et al., 2008). The sample for this analysis includes 2,048 participants who had complete data on all study variables.

Measures

Neurological Soft Signs (NSS)

NSS were measured during a neurological examination done according to the CPP protocol. Board certified pediatricians performed the exam, blinded to the child's medical record, under the supervision of a senior board certified pediatric neurologist. The CPP exam assessed 3 functional subgroups of NSS: abnormalities in motor coordination, sensory functions, and involuntary movement.

Motor coordination signs consisted of the following items: Dysdiadochokinesia, dysmetria and ataxia. Dysdiadochokinesia is the difficulty in performing rapid alternating movement of the hands and feet in a smooth and fluent way. Dysmetria is the difficulty in accurately positioning a limb, especially in the terminal part during movement. Ataxia is the failure to synthesize component muscular actions into a smooth and accurate movement. These signs were elicited by asking participants to perform the following tests: rapid alternating movement, finger to nose, heel to knee with eyes open and closed, finger pursuit, rapid individual finger movement, and complex activities such as fastening buttons or zippers, tying shoes, writing, or picking up small objects.

Sensory neurological soft signs consisted of: right and left identification, astereognosis, and position sense. A child was asked to perform these tests with emphasis on the right or left hand, and their initial response was recorded. Astereognosis, which is the inability to identify three-dimensional object by touch without visual input, was tested by placing visually recognizable objects one at a time into the child's hand and asking him/her to identify them with their eyes closed. Position sense was performed using two tests: 1) passive movement of the great toe, where the examiner grasps the big toe by the sides and passively moves it through a small arc. The child is then asked to give the direction of the movement during the motion on at

least five trials. 2) Location of a finger in space, where the examiner places one of the child's index fingers in space and then, with the child's eyes closed, asks them to touch it with his/her other index finger.

Involuntary movement consisted of mirror movement and tremors. Mirror movement is involuntary movement in the hand opposite the hand engaged in a simple task. Children were asked to do rapid thumb-forefinger apposition in one hand while the examiner observed the other hand to detect mirror movement. This was repeated for the other hand. Tremors were identified as spontaneous tremors, which are tremors present at rest, and also tremors associated with maintenance of posture.

NSS were measured using a clinical neurological examination that is substantially similar to the type currently used in research (Buchanan & Heinrichs, 1989; Chen et al., 1995; Convit et al., 1994; Jahn et al., 2006; Krebs et al., 2000; Vreeling et al., 1993). The specific abnormalities counted in our measure of NSS have considerable overlap with abnormalities assessed in modern batteries, namely the Cambridge Neurological Inventory (Chen et al., 1995) and the Krebs (Krebs et al., 2000). The Neurological Evaluation Scale (Buchanan & Heinrichs, 1989), for example, included extra-pyramidal signs and reflexes that are often not defined as soft signs, or signs that are commonly detected in psychotic patients rather than in the general population, limiting its use in population studies. Compared to the Brief Motor Scale (Jahn et al., 2006), which only includes items of motor coordination, our measure included sensory and involuntary movement items (Supplemental Table 1.4).

Grouping strategies of NSS are often based on presumed neuro-anatomical substrate, which is debatable in the absence of defined focal lesions (Sanders & Keshavan, 1998). Empirically-based groups using latent variable approaches showed inconsistent results (Malla et

al., 1997; Schröder et al., 1991). Therefore, a count of the number of NSS exhibited by each child better represents the overall severity of neurologic dysfunction, and avoids the pitfalls of using categories of NSS that are not biologically or empirically supported. The count measure used here was capped or truncated at 2 given the small number of children that exhibited 3 or 4 signs (n=7).

Attention Deficit Hyperactivity Disorder

Lifetime ADHD was assessed in the adult offspring of the CPP at follow-up studies using standardized interviews based on the Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, & Ratcliff, 1981). Diagnoses were assigned based on the Diagnostic and Statistical Manual of Mental Disorders (4th ed.;DSM-IV) (American Psychiatric Association, 2000) criteria: 1) the presence of six or more hyperactive and/or inattentive symptoms that persisted for at least 6 months, were maladaptive, and inconsistent with developmental level; 2) some impairment from the symptoms evident in two or more settings (i.e. school and home); and 3) presence of clear evidence of clinically significant impairment. The DIS instrument asks subjects to report on "what you were like in your first few years at school, say from age 6 to 10…" to ascertain that the symptoms occurred before or by age 7, and then queries about 18 individual symptoms of inattention and hyperactivity; specific age of onset was not collected for all participants. ADHD diagnoses for all subjects were assigned based on full DSM-IV criteria for number of qualifying symptoms, occurrence in multiple settings, and evidence of clinically significant impairment. ADHD inattentive subtype diagnosis was given for participants who reported 6 or more symptoms of inattention, but not enough hyperactivity/impulsivity symptoms, Hyperactive-subtype was assigned to participants who reported 6 or more hyperactivity/impulsivity symptoms

but not enough inattention symptom, and the combined subtype was given to those who reported 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity.

Other covariates

We adjusted for variables that could be potential confounders including low birth weight defined as birth weight less than 2.500 Kg (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Breslau et al., 2000), socioeconomic status (SES) (Chin-Lun Hung et al., 2015; Heikura U, 2008; Koutra, 2012; Russell, Ford, & Russell, 2015), race, sex, and risk factors for brain injury or aberrant neurodevelopment.

Family SES at age seven was a weighted percentile of each head of household's education, occupation, and income relative to the US population,(Myrianthopoulos & French, 1968). SES scores were divided into 3 categories corresponding to low (0-33%), medium (>33%-66%) and high SES (>66%).

History of pregnancy or delivery complications, low Apgar scores, fetal resuscitation after birth, and ICU admission were adjusted for, as they are potential causes of brain injury due to ischemic, or traumatic processes (Leviton & Nelson, 1992; Nelson & Leviton, 1991). In addition, we adjusted for maternal history of psychiatric or neurologic disorders, maternal smoking (Langley, Rice, van den Bree, & Thapar, 2005), and exposure to prescription drugs during pregnancy, which are potential risk factors for aberrant neurodevelopment.

Statistical Analysis

We performed a series of logistic regression models to evaluate the association between NSS and the risk of lifetime ADHD and its subtypes, adjusting for all covariates mentioned above.

To test if NSS would specifically predict the risk of ADHD hyperactive subtype, we used a special case of generalized linear models (GLM) often used to simultaneously analyze multiple source outcomes (Fitzmaurice, 2011; Horton & Fitzmaurice, 2004). The method involved creating a dataset with multiple records for each participant formed by stacking the outcomes for the subtypes of ADHD; in addition, a variable is created that identifies the particular subtype. Subsequently, interaction terms between this variable that identifies the subtype and NSS (and all other covariates) were included in the model. The inclusion of the interaction terms permits a test of the specificity of the association. A Wald test was performed to examine whether NSS would specifically predict the risk of the hyperactive subtype vs. the other subtypes.

To support the validity of the diagnosis of ADHD, we compared the diagnosis to behavioral ratings that were collected at age 7. Trained psychologists evaluated children behaviors at age 7. These behaviors included hyperactivity, short attention span, impulsivity and low frustration tolerance, which are commonly reported symptoms in patients with ADHD. We performed a chi-square test to compare the prevalence of these behavioral ratings individually and combined between participants with and without ADHD diagnosis.

All statistical tests were two-tailed, and alpha was set at 0.05.

Results

This study sample included 2,048 participants. There were 966 (47.2%) males and 1082 (52.8%) females in the total sample. Approximately 50% of the sample had a socioeconomic status (SES) in the medium range and the majority was White. 8.2% had a birth weight less than 2.5 kg, 35.3% had any pregnancy or delivery complication, 12.7% had an Apgar score less than 7 and 6.2% had a history of resuscitation at birth. 16.3%, 2.8% and 57.0% had a history of

maternal neurologic or psychiatric disorder, in-uetro exposure to prescription drugs, and maternal smoking respectively.

The prevalence of ADHD was 10.88% (n= 223), 15.5% (n=150) in males, and 6.7% (n=73) in females, with a male: female ratio of 2.31:1. Rates of ADHD among strata of risk factors are also shown in table 2.1. Prevalence of ADHD was high (> 12%) among males (15.5%), participants with low SES (18.7%), Black and other ethnicity (13.7%), participants with any history of pregnancy or delivery complication (12.7%), participants with Apgar score less than 7 (17.6%), those who were resuscitated at birth (15.9%), exposed to prescription drugs (18.6%) and finally those with history of maternal smoking (12.2%) (Table 2.1).

Table 2. 1 Characteristics of the New England Family Study (NEFS) participants (N=2,048) and distribution of ADHD diagnosis

	ADHD n (%)	Total n (%)
Sex		
Male	150 (15.5)	966 (47.2)
Female	73 (6.7)	1082 (52.8)
Paternal socioeconomic status		
High	28 (4.6)	613 (29.9)
Medium	121 (11.6)	1039 (50.7)
Low	74 (18.7)	396 (19.3)
Age at adult follow-up interview (years)		
26-35	47 (12.9)	364 (17.8)
36-45	165 (10.3)	1606 (78.4)
45+	11 (14.1)	78 (3.8)
Race/Ethnicity		
White	180 (10.4)	1736 (84.8)
Black	38 (13.0)	293 (14.3)
Other	5 (26.3)	19 (1.0)
Birth weight		
≥ 2.5 Kg	207 (11.0)	1880 (91.8)
< 2.5 Kg	16 (9.5)	168 (8.2)

Any pregnancy or delivery complication	92 (12.7)	723 (35.3)
Apgar at 5 min < 7	46 (17.6)	261 (12.7)
Resuscitation at birth	20 (15.9)	126 (6.2)
Maternal history of neurologic or psychiatric disorders	36 (10.8)	334 (16.3)
Exposure to drugs during pregnancy	11 (18.6)	59 (2.8)
Maternal smoking	143 (12.2)	1168 (57.0)

The prevalence of any NSS was 26.20% and the total number of NSS signs exhibited by a child ranged from 0 to 4. The most common sign was poor left-right identification (21.4%) and the least common was ataxia (0.1%) (Table 2.2).

Table 2. 2 Distribution of Neurological Soft Signs (NSS) overall and by sex (N=2,048)

NSS Count	Total n (%)
0	1511 (73.8)
1	468 (22.9)
2	62 (3.0)
3	6 (0.3)
4	1 (0.1)
Motor	
Ataxia	3 (0.1)
Dysdiadochokinesia	51 (2.5)
Dysmetria	17 (0.8)
Sensory	
Astereognosis	15 (0.7)
Left_right identification	439 (21.4)
Position sense	39 (1.9)
Involuntary Movement	
Mirror movement	42 (2.1)
Tremor	8 (0.4)

The distributions of ADHD and its subtypes according to the number of NSS are shown in table 3. The prevalence of any ADHD diagnosis was 8.7% in those without signs, compared to 15.8% and 24.6% in those with 1 and 2+ signs respectively. The prevalence of ADHD-hyperactive subtype was 2.8% in those without NSS compared to 5.8% and 5.8% in those with 1 and 2+ signs. The prevalence of ADHD-inattentive subtype was 3.4% in those without NSS compared to 4.9% and 10.1% in those with 1 and 2+ signs respectively. Finally, The prevalence of the combined-subtype of ADHD was 2.6% compared to 5.1% and 8.7% in those with 1 and 2+ signs respectively (Table 2.3).

Table 2. 3 ADHD and its subtypes by number of NSS (N=2,048)

NSS Count	ADHD –hyperactive n (%)	ADHD – inattentive n (%)	ADHD-combined n (%)	Any ADHD n (%)
0	42 (2.8)	51 (3.4)	39 (2.6)	132 (8.7)
1	27 (5.8)	23 (4.9)	24 (5.1)	74 (15.8)
2+	4 (5.8)	7 (10.1)	6 (8.7)	17 (24.6)
Total	73 (3.6)	81 (3.9)	69 (3.4)	223 (10.9)

The results of the logistic regression analysis are shown in table 2.4. The risk of any ADHD diagnosis increased by 70% (CI= 1.4, 2.2), 60% (CI= 1.2, 2.2) for ADHD-hyperactive subtype, 50% (CI= 1.1, 2.1) for the inattentive subtype and finally 80% (CI= 1.3, 2.6) for the combined subtype as the number of NSS increased by one unit (Table 2.4).

Table 2. 4 The association between NSS and the risk of ADHD and its subtypes (N=2,048)

	ADHD – hyperactive	ADHD – inattentive	ADHD - combined	Any ADHD
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NSS count	1.6 (1.2, 2.2)	1.5 (1.1, 2.1)	1.8 (1.3, 2.6)	1.7 (1.4, 2.2)

Note: All models controlled for age of the child when NSS were measured, age at interview, race, sex, paternal socioeconomic status, birth weight, study site, pregnancy and delivery complications, Apgar scores at 5 minutes, resuscitation at birth, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy.

Although NSS appeared to be associated with a higher risk of the combined subtype followed by the hyperactive subtype and finally the inattentive subtype, NSS did not predict a statistically higher risk of ADHD- hyperactive subtype when compared to other subtypes (test of homogeneity of odds ratios, $X^2_{(2)} = 0.60$, P= 0.74).

Finally, table 2.5 shows the frequency distribution of ADHD diagnosis between participants with and without behaviors of hyperactivity, inattention, impulsivity and low frustration tolerance that were assessed at age seven. The frequency of hyperactivity at age seven was 13.9% among those with ADHD diagnosis compared to 8.2% among participants with no ADHD diagnosis. Similarly, the frequency of inattention at age seven was 18.8% among participants with ADHD compared to 8.8% among those without the diagnosis. Low frustration tolerance and impulsivity showed similar trends. In general, the frequency of these behavioral ratings was twice as high among participants with ADHD compared to those without ADHD. In addition, the frequency of having 3 or more behavioral ratings was twice as high among those with ADHD diagnosis, 9.9% compared to 4.8% in those without the diagnosis ($X^2_{(1)} = 9.93$, P = 0.001).

Table 2. 5 Comparison of the distribution of behavioral ratings at age 7 by ADHD diagnosis status (N=2,048)

Behavioral profile	Hyperactivity	Inattention	Low frustration tolerance	Impulsivity	Inattention+hyperactivity	3+ behaviors	Total
ADHD	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Yes	31 (13.9)	42 (18.8)	54 (24.2)	33 (14.8)	13 (5.8)	22 (9.9)	223
No	149 (8.2)	161 (8.8)	326 (17.9)	148 (8.1)	47 (2.6)	88 (4.8)	1825
$X^2_{(1)}$	22.28***	1390.31***	809.17***	1387.02***	7.39 *	4.82 **	

* P< 0.01

** P< 0.001

*** P< 0.0001

Discussion

This analysis combines data from two studies of the NEFS project, a series of follow up studies of the adult offspring of the Providence and Boston CPP cohort. Our analysis provided uniqe opportunity to study the association between NSS and subtypes of ADHD, utilizing a community sample that was followed prospectively. In this community sample, NSS were measured in childhood and ADHD was measured using standardaized instruments during adulthood. Our analysis adjusted for a wide array of potential confounding perinatal factors that were collected prospectively.

Our results showed that NSS were associated with a 70% increase in the risk for ADHD with each unit increase in NSS. Prior studies examined the prevalence of NSS among participants with an established diagnosis of ADHD in clinical samples. In addition, these studies did not account for important confounding factors, such as risk factors for brain injury and aberrant development (Cardo et al., 2008; Gong, Xie, Chen, Zhang, & Wang, 2015; Kaneko, Yamashita, & Iramina, 2016; Pasini & D'Agati, 2009; Patankar et al., 2012).

The underlying mechanisms linking NSS and ADHD are not fully known. They are both hypothesized to be signs of neuronal immaturity or they possibly share an anatomical substrate (Pasini & D'Agati, 2009). A shared anatomical substrate is supported by the findings that NSS improved by psychostimulants, a first line treatment for ADHD (Hrtanek et al., 2015; Lerer & Lerer, 1976; Lerer et al., 1977). However the improvement in NSS did not correlate with the improvement in ADHD symptoms. These findings do not go against an association between NSS and ADHD, but may suggest that the differential effect of psychostimulants on NSS and ADHD is possibly duration or dose-dependent. This argues against reverse causation, where deficits of attention and hyperactivity in participants with ADHD give rise to NSS.

Furthermore, we examined the association between NSS and subtypes of ADHD. Our results showed that NSS are associated with increased risk for all subtypes of ADHD ranging from 50-80%; the risk for the combined subtype was the highest followed by the hyperactive subtype and lastly the inattentive subtype. However, the differences between these effect sizes were small and not statistically discernible. Specifically, the association between NSS and the risk of the hyperactive subtype was not statistically different than the corresponding associations for the other subtypes.

Because of the lack of specificity of the effect of NSS on ADHD subtypes, we conjecture that the shared underlying mechanism for the association between NSS and ADHD extends beyond alteration in the neural networks for motor control inhibition as previously suggested (Pasini & D'Agati, 2009). Furthermore, it supports the evidence that argues against the validity of ADHD subtypes. Many studies have shown that individuals with ADHD may experience symptoms of different subtypes of the disorder at different stages of their lives (Faraone et al., 1998; Geurts et al., 2005; Lahey et al., 2005). In addition, Faraone and colleagues did not find substantive cognitive or psychosocial differences between the different subtypes (Faraone et al., 1998). This implies that these subtypes are not distinct disorders but are arguably different faces of the same disorder. Hence, the change in nomenclature from subtypes to presentations in DSM-5 (American Psychiatric Association, 2013). Therefore, research examining the effectiveness of interventions targeting NSS should include all subtypes of ADHD.

A limitation of our study is that information on ADHD was collected retrospectively from the adult offspring who were on average in their third decade of life when interviewed. Therefore, we compared the ADHD diagnosis to behavioral ratings suggestive of ADHD measured at age 7. Specifically, our results showed that the frequencies of the following

behavioral ratings: inattention, hyperactivity, impulsivity, and low frustration tolerance, which are considered to be core symptoms of ADHD, were approximately twice as high among those who had the diagnosis of ADHD. These results support the validity of retrospective reports of ADHD in our sample. This is in addition to the already available literature on the validity of retrospective reports of ADHD in general (Faraone et al., 2000; Glockner-Rist et al., 2013; Murphy & Schachar, 2000).

As with other prospective cohort studies, our study could have been biased due to attrition. In our study the follow up cohort was only a fraction of the original sample; however, basic demographic variables and distribution of exposure and confounders were similar to that of the original sample (Supplemental Table 2.6). Further, the prevalence of ADHD in our sample was 10.88%, similar to prevalence reported in other community samples (Brown et al., 2001; Faraone, Sergeant, Gillberg, & Biederman, 2003). The distribution of ADHD subtypes was also similar to other reports, with the most common subtype the inattentive subtype (Willcutt et al., 2012).

In summary, NSS, manifestations of a minor cerebral dysfunction caused by either brain injury or aberrant neurodevelopment, were found to increase the risk for ADHD. These results are based on data from a longitudinal design where NSS were measured in childhood and ADHD was diagnosed using standardized instrument in a community sample. However, there was no evidence that the association between NSS and the risk of the hyperactive subtype was different than the corresponding associations for the other subtypes.

Finally, a potential clinical implication of our study is to promote the incorporation of NSS assessment into the clinical evaluation of children at risk for ADHD. More research is needed to understand the underlying mechanisms for this association and explore the

effectiveness of these interventions targeting NSS, such as occupational and physical therapy (Blank et al., 2012) as adjunct treatment for ADHD for optimal control of symptoms or alternative treatment options if pharmacotherapy is not desirable.

Supplemental Material

Supplemental Table 2. 6 A comparison between the CPP sample that underwent neurological exam at age 7, the Boston and Providence branch, and the complete case analysis NEFS sample in key demographics and exposure distribution

	All children with neurological exam at age 7 (n = 41,911)	Children with neurological exam at age 7 from Boston and Providence only (n = 11,076)	NEFS participants (LD +TTURC) (n= 2,048)
	Prevalence	Prevalence	Prevalence
Female	49.5	48.9	53.4
Male	50.6	51.1	46.6
Birth weight < 2.5 Kg	9.3	8.0	9.2
SES			
High	23.5	35.4	29.9
Medium	49.2	50.6	50.7
Low	24.8	14.0	19.3

Prevalence of one or more NSS	32.1	28.87	26.6
Motor			
Ataxia	0.3	0.6	0.15
Dysdiadochokinesia	2.8	4.3	2.49
Dysmetria	0.6	1.3	0.83
Awkwardness	0.04	0.03	0.0
Sensory			
Astereognosis	1.1	0.7	0.73
R-L identification	26.0	21.6	21.45
Involuntary movement			
Mirror movement	2.1	3.0	2.05
Tremor	0.4	0.9	0.39

Chapter 3: Neurological Soft Signs and Major Depressive Disorder

Neurological Soft Signs and Major Depressive Disorder

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Abstract

Background. The role of Neurological soft signs (NSS) in depressive disorders has only been investigated in small studies using clinical samples, and without accounting for severity measures of depression. Children with NSS have been found to have higher rates of depressive disorders due to the daily challenges they face, but the effect of NSS on risk of depression in adulthood is unknown. In this analysis we use a longitudinal design, to examine whether NSS predict the risk of lifetime depression in different stages of the life cycle and outcomes suggestive of severity, such as suicidal ideations and attempts.

Method. We analyzed data from 2,317 adult offspring who participated in the New England Follow up Studies of the Collaborative Perinatal Project (CPP), to study the risk of lifetime major depressive disorder (MDD) using a Cox proportional hazard model while adjusting for demographics, and risk factors for brain injury and aberrant neurodevelopment. We used logistic regression models to examine the effect of NSS on the risk of suicidal ideations and attempts. In addition, we examined whether NSS were differentially associated with depression in childhood and adolescence vs. adulthood.

Results. NSS were not associated with increased risk for MDD (HR= 0.95, 95% CI (0.83-1.10), or with outcomes of severity such as suicidal ideations (OR = 1.14, CI (0.83-1.10)) or attempts (OR= 1.59, CI (0.92-2.74)). Further, NSS were not associated with depression in any stage of the life cycle, whether in childhood (HR=0.96, CI=(0.71, 1.10)), adolescence (HR= 0.97, CI (0.76, 1.25)) or adulthood (HR= 0.81, CI (0.63, 1.00)).

Conclusion. Our results did not find an association between NSS and MDD at any stage of life. Furthermore, NSS did not predict severity outcomes, such as suicidal ideations or attempts. These results suggest that NSS and MDD are possibly neurobiologically different.

Introduction

Neurological soft signs (NSS) are neurological abnormalities that are thought to be manifestations of a minor non-specific cerebral dysfunction that could be either localized or diffuse (Dazzan & Murray, 2002). They include poor motor coordination, sensory perceptual difficulties, and involuntary movements and are often detected during a neurological examination. The minor cerebral dysfunction, manifested by NSS, is often hypothesized to be due to factors such as brain injury that occurred perinatally, or an aberrant neurodevelopment that is genetic in origin (Nichols & Chen, 1981), or due to intrauterine exposure to toxins (Ferriero, 2004).

NSS may cause major depressive disorders through two mechanisms: an underlying neurobiological mechanism, or the psychological impact of navigating these deficits, or a combination of both. A neurobiological link between NSS and depression remains unclear. NSS could be manifestations or correlates of insults or injury of brain regions that are involved in mood regulation leading to increased biological predisposition for depression. In terms of psychological impact, children with NSS may struggle with performing tasks efficiently in different settings interfering with self-care and socialization. This may increase their frustration and feelings of inadequacy leading to rejection and victimization from peers and eventually leading to depressive symptoms (Campbell, Missiuna, & Vaillancourt, 2012). For instance, motor coordination deficits and disorders have been found to be associated with low self esteem, depression and anxiety by late childhood or adolescence (Piek et al., 2010) (Shaffer, 1978). There is also evidence that NSS, particularly the motor deficits, and the difficulties associated with them may persist into adulthood (Losse et al., 1991; Shafer et al., 1986), resulting in continuation of low self-esteem and clinically significant depression (Poole et al., 2016).

However, most of these studies linked only motor deficits rather than other subgroups of NSS like sensory and involuntary movement signs. And none of the studies have looked at whether NSS will differentially increase the risk of depression in childhood relative to adolescence or adulthood, when the risk may decrease or disappear.

On the contrary, some studies have not found an association between NSS and depression; instead, they found NSS to discriminate between patients with psychotic and bipolar disorders from patients with major depressive disorder and healthy controls (Zhao et al., 2013). In general, NSS were found to be more prevalent in patients with psychotic disorders compared to those with mood disorders (Boks et al., 2004; Leask, Done, & Crow, 2002; Sewell et al., 2010). Most of these studies were of smaller scale, using clinical samples and a cross sectional design and did not examine the association between NSS with severity outcomes of depressive disorders, where manifestations of biological system dysfunction such as NSS may be more relevant. In addition, they did not control for important confounders like perinatal adverse events.

To the best of our knowledge, this is the first study to use a longitudinal design with an adequate sample size, to examine if NSS predict the occurrence of major depressive disorder, and whether NSS predict severity outcomes of depression, such as suicidal ideations and attempts, while controlling for important confounding factors such as perinatal factors. In addition, we examined if NSS would increase the risk of depression during specific stages of the life cycle, specifically childhood and adolescence.

Methods

Study Population

Our sample includes participants from the New England Family Studies project (NEFS), a series of follow up studies that followed the adult offspring of the Collaborative Perinatal Project [CPP]. The CPP started as a multi site prospective cohort study that recruited 48,197 pregnant women at 12 university-affiliated medical centers between 1959 and 1966. The CPP followed women through pregnancy and delivery and their offspring for the first 7 years of life (Broman, 1984b; Niswander & Gordon, 1972). The NEFS was established to locate and interview the adult CPP offspring at the Providence, Rhode Island and Boston, Massachusetts's sites. NEFS included multiple follow up studies all of which included structured diagnostic interviews for major depression (Gilman et al., 2003; Gilman et al., 2008; Loucks et al., 2012). Selection of Providence and Boston NCPP births for the adult follow-up studies occurred over multiple phases, in each a stratified random sample was drawn from the entire cohort. Between 1983-1989, 1068 eligible subjects with and without pregnancy/delivery complications were selected to investigate the effect of such complications on risk of developing psychiatric disorders, of those only 693 were interviewed (Klebanoff, Zemel, Buka, & Zierler, 1998). Between 1995 -1999, 1056 subjects with and without potential learning disabilities were selected to study the typologies and determinants of these disorders, of those only 720 were interviewed (Buka et al., 1993). Finally, between 1999 -2009, a multi-stage sampling procedure was done to select 2271 eligible participants based on smoking status and educational attainment. 1625 were interviewed to identify determinants of smoking, its life course and response to treatment (Gilman et al., 2008). Of the above 1625 participants, 617 participants were selected to study pathways between education and health in adulthood. All interviews were conducted under the oversight of the Institutional Review Boards of the Harvard School of Public Health and Brown University.

To investigate the risk of depressive disorders, participants had to have complete data on our measure of NSS at age 7, lifetime MDD diagnosis, and additional covariates described below. Out of the 2,500 participants in NEFS, our analysis includes 2317 participants who had complete data on all the study variables. Of those, 190 participated in two studies, 96 participated in 3 studies and 16 participated in 4 studies.

Measures

Neurological Soft Signs (NSS)

NSS were measured during a neurological examination done according to the CPP protocol. Board certified pediatricians performed the exam, blinded to the child's medical record, under the supervision of a senior board certified pediatric neurologist. The CPP exam assessed 3 functional subgroups of NSS: abnormalities in motor coordination, sensory functions, and involuntary movement.

Motor coordination signs consisted of the following items: dysdiadochokinesia, dysmetria, ataxia, and awkwardness. Dysdiadochokinesia is the difficulty in performing rapid alternating movement of the hands and feet in a smooth and fluent way. Dysmetria is the difficulty in accurately positioning a limb, especially in the terminal part during movement. Ataxia is the failure to synthesize component muscular actions into a smooth and accurate movement. These signs were elicited by asking participants to perform the following tests: rapid alternating movement, finger to nose, heel to knee with eyes open and closed, finger pursuit, rapid individual finger movement, and complex activities like fastening buttons or zippers, tying shoes, writing, or picking up small objects.

Sensory neurological soft signs consisted of: right and left identification, astereognosis, and position sense. A child was asked to perform these tests with emphasis on the right or left

hand, and their initial response was recorded. Astereognosis, which is the inability to identify three-dimensional object by touch without visual input, was tested by placing visually recognizable objects one at a time into the child's hand and asking him/her to identify them with their eyes closed. Position sense was performed using two tests: 1) passive movement of the great toe, where the examiner grasps the big toe by the sides and passively moves it through a small arc. The child is then asked to give the direction of the movement during the motion on at least five trials. 2) Location of a finger in space, where the examiner places one of the child's index fingers in space and then, with the child's eyes closed, asks them to touch it with his/her other index finger.

Involuntary movement consisted of mirror movement and tremors. Mirror movement is involuntary movement in the hand opposite the hand engaged in a simple task. Children were asked to do rapid thumb-forefinger apposition in one hand while the examiner observed the other hand to detect mirror movement. This was repeated for the other hand. Tremors were identified as spontaneous tremors, which are tremors present at rest, and also tremors associated with maintenance of posture.

NSS were measured using a clinical neurological examination that is substantially similar to the type currently used in research (Buchanan & Heinrichs, 1989; Chen et al., 1995; Convit et al., 1994; Denckla, 1985; Jahn et al., 2006; Krebs et al., 2000; Vreeling et al., 1993). The specific abnormalities counted in our measure of NSS have considerable overlap with abnormalities assessed in modern batteries commonly used in research, namely the Cambridge Neurological Inventory (Chen et al., 1995) and the Krebs (Krebs et al., 2000). The Neurological Evaluation Scale (Buchanan & Heinrichs, 1989), for example, included extra-pyramidal signs and reflexes that are often not defined as soft signs, or signs that are commonly detected in psychotic patients

rather than in the general population limiting its use in population studies. Compared to the Brief Motor Scale (Jahn et al., 2006), which only includes items of motor coordination, our measure included sensory and involuntary movement items (Supplemental Table 1.4).

Grouping strategies of NSS are often based on presumed neuro-anatomical substrate, which is debatable in the absence of defined focal lesions (Sanders & Keshavan, 1998). Empirically-based groups using latent variable approaches showed inconsistent results (Malla et al., 1997; Schröder et al., 1991). Therefore, a count of the number of NSS exhibited by each child better represents the overall severity of neurologic dysfunction, and avoids the pitfalls of using categories of NSS that are not biologically or empirically supported. The count measure used here was capped at 2 given the small number of children that exhibited 3 or 4 signs (n=9).

Major Depressive Disorder

Major depressive disorder was assessed by trained interviewers using the Diagnostic Interview Schedule (DIS) (Robins et al., 1981). The DIS is a structured diagnostic interview based on the DSM-III or DSM-IV criteria. The DIS has been shown to have good reliability in assessing depression in community samples (Erdman et al., 1987; Wittchen et al., 1989). Changes in diagnostic criteria for depression between DSM-III and DSM-IV were minimal and did not result in significant differences in the identification of cases in epidemiologic samples (Eaton et al., 1997; Gilman, Kawachi, Fitzmaurice, & Buka, 2002).

Participants were asked how old they were when they first experienced a depressive episode to assess age at onset. For those who participated in more than one study, the earliest age of onset reported was considered as age of onset in our analysis.

Participants were also asked if they thought about suicide or had a plan during a depressive episode and whether they attempted suicide while depressed.

Other covariates

We adjusted for a wide range of variables that could be potential confounders including low birth weight defined as birth weight less than 2.500 Kg (Breslau et al., 2000), socioeconomic status (SES) (Chin-Lun Hung et al., 2015; Heikura et al., 2008; Koutra, 2012) , race, sex, risk factors for brain injury or aberrant neurodevelopment and NEFS study. Family SES at age seven was a weighted percentile of each head of household's education, occupation, and income relative to the US population (Myrianthopoulos & French, 1968). SES scores were divided into 3 categories corresponding to low (0-33% of the distribution), medium (34%-66%) and high (>66%) SES.

History of pregnancy or delivery complications, low Apgar scores, fetal resuscitation after birth, and ICU admission were adjusted for, as they are potential causes of brain injury due to ischemic, or traumatic processes (Leviton & Nelson, 1992; Nelson & Leviton, 1991). In addition, we adjusted for maternal history of psychiatric or neurologic disorders, maternal smoking, and exposure to prescription drugs during pregnancy, which are potential risk factors for aberrant neurodevelopment.

Finally, as mentioned above, each of the NEFS follow up studies had different inclusion/ exclusion criteria based on the specific objectives of these studies and therefore we controlled for which study the participant contributed to.

Statistical Analysis

To study whether NSS at age 7 predict risk of lifetime diagnosis of MDD, a Cox proportional hazards model was used with time until diagnosis of MDD as the outcome to account for age of onset. Subjects contribute person-years to the analysis from age 7 until the onset of depression, loss to follow-up, death or the age at interview. Use of hazard ratios account

for the occurrence of MDD and age of onset, while accounting for the variable follow-up period among subjects and finely adjusting for the potentially confounding effects of other variables (e.g. low birth weight, SES, race, sex, risk factors for brain injury or aberrant neurodevelopment).

To examine the hypothesis that NSS would predict a higher risk of MDD in childhood relative to adolescence or adulthood, a Cox proportional hazards model was used that allowed the hazard ratio for NSS to vary across four age of onset groups, <15, 15-25, 26-35, and >35 years; this analysis was implemented by including interaction terms between NSS and three indicator functions for the age of onset groupings.

Logistic regression models were used to study the association between NSS count and suicide ideations and attempts. Results of the Cox and logistic models are reported as hazard ratios (HR) and odds ratio (OR) for NSS, respectively and 95% confidence interval (CI).

Results

This study sample included 2,317 adult participants who were interviewed between the ages of 17 and 48, more than half of our sample was interviewed between the ages of 36 and 45 years. Our sample had 1,079 males and 1,238 females, with a socioeconomic status within the medium range, and the majority was white (82.2%). The prevalence of low birth weight was 9.2%, and of any pregnancy or delivery complication was 37.0%. Of the newborn offspring, 9.1% had ICU admission and 6.4% had resuscitation at birth. There was 17.4% who had a maternal history of neurologic or psychiatric disorder, and 56.9% had mothers who smoked during pregnancy (Table 3.1).

Table 3. 1 Characteristics of the New England Family Studies' participants (n=2,317)

	n [%]
Sex	
Males	1,079 (46.6)
Females	1,238 (53.4)
Paternal socioeconomic status	
High	646 (27.9)
Medium	1,185 (51.1)
Low	486 (21.0)
Age at adult follow-up interview (years)	
17-25	272 (11.7)
26-35	380 (16.4)
36-45	1,590 (68.6)
45+	75 (3.2)
Race/Ethnicity	
White	1,905 (82.2)
Black	390 (16.8)
Other	22 (0.9)
Birth weight	
≥ 2.5 Kg	2,104 (90.8)
< 2.5 Kg	213 (9.2)

Any pregnancy and delivery complications	858 (37.0)
Weeks of gestation < 37 weeks	146 (9.3)
Apgar score at 1 min < 7	593 (25.6)
Apgar at 5 min < 7	324 (14.0)
Resuscitation at birth	148 (6.4)
ICU admission	211 (9.1)
Maternal history of neurologic or psychiatric disorders	403 (17.4)
Exposure to drugs during pregnancy	69 (3.0)
Maternal smoking	1,318 (56.9)

The prevalence of having any NSS was 26.7 %, the total number of NSS signs exhibited by a child ranged from 0-4, with the most common being left/right identification (22.2%) and the least common Ataxia (0.13%) (Table 3.2).

Table 3. 2 Distribution of Neurological soft signs in New England Family Studies sample (n=2,317)

NSS	Total
	n [%]
Count	
0	1,699 (73.3)
1	538 (23.2)
2	71 (3.1)
3	8 (0.4)
4	1 (0.0)
Motor	
Ataxia	3 [0.13]
Dysdiadochokinesia	51 [2.20]
Dysmetria	19 [0.82]
Sensory	
Astereognosis	18 [0.77]
Left_right identification	515 [22.23]
Position sense	49 [2.11]
Involuntary Movement	
Mirror movement	45 [1.94]
Tremor	8 [0.35]

Out of 2317 participants, 702 (30.3%) met the criteria for lifetime major depressive disorder. Prevalence of suicidal ideations was 15.2% (n= 353) and the prevalence of suicide attempts during a depressive episode was 8.7% (n=202)

The prevalence of lifetime major depressive disorder among those with no NSS as children was 31.13% compared to 28.25% if they exhibited one sign, 30.00% in those with at least two signs, while the prevalence of suicidal ideation was respectively 15.36%, 15.42% and 11.25%. Similarly, the prevalence of suicide attempts was 9.60 % in those exhibiting one sign, 5.00% in those exhibiting at least two signs, compared to 8.60 % in those with no signs at all (Table 3.3).

Table 3. 3 Lifetime MDD, age of onset and suicidal outcomes per count of NSS in the NEFS sample (n=2,317)

NSS Count	Lifetime MDD	Age of onset	Suicidal ideations	Suicidal attempts
	n (%)	Mean (SD)	n (%)	n (%)
0	526 (30.96)	23.3 (9.0)	261 (15.36)	146 (8.60)
1	152 (28.25)	22.6 (9.9)	83 (15.42)	52 (9.60)
2+	24 (30.00)	22.9 (9.7)	9 (11.25)	4 (5.00)
Total	702 (30.30)	23.1 (9.2)	353 (15.23)	202 (8.72)

The mean age of onset of major depressive disorder in those without NSS was 23.3 (SD= 9.0), while it was 22.6 (SD= 9.9) and 22.9 (SD= 9.7) for those with 1 and 2+ signs respectively (Figure 3.1).

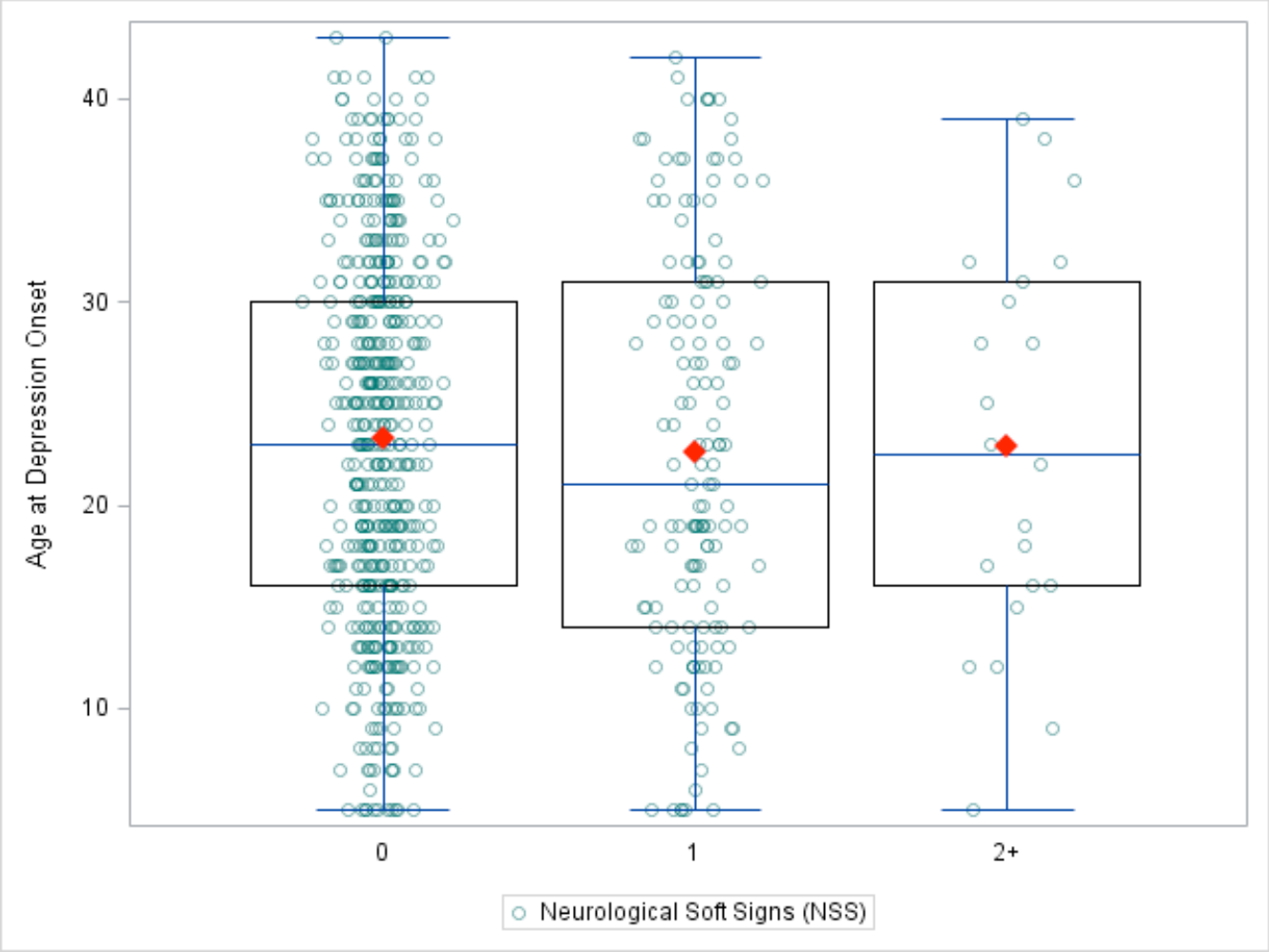

Figure 3. 1 Age of onset of major depressive disorder per count of neurological soft signs in New England Family Studies (N= 2,317)

The risk of lifetime depression in those with one sign was 0.95 the risk of those with no signs (HR=0.95; CI =0.83-1.1). Similarly, the odds of having suicidal ideations (OR = 1.14, CI (0.84-1.55)) or attempts (OR= 1.59, CI (0.92-2.74)) were not significantly different as the number of NSS increased compared to those with no signs (Table 3.4).

Table 3. 4 The association between neurological soft signs and the risk of major depressive disorder and suicidal outcomes in New England Family Studies (n=2,317)

	MDD	Suicidal ideations	Suicidal attempts
	HR (95% CI)*	OR (95% CI)*	OR (95% CI)*
NSS count	0.98 (0.85-1.12)	1.17 (0.86-1.60)	1.60 (0.92- 2.78)

Note: All models controlled for age of the child when NSS were measured, race, sex, paternal socioeconomic status, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, ICU admission, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy. Logistic models controlled for age of interview and age of onset, in addition.

When specifically examining whether NSS would increase the risk of major depressive disorder in early childhood relative to adolescence or adulthood, NSS did not predict the risk of depression in any stages of the life cycle (Table 3.5) and this risk did not differ significantly between any of the 4 age groups considered ($X^2_{(3)} = 4.99$, P= 0.172).

Table 3. 5 The association between neurological soft signs and age of onset of major depressive disorder in New England Family Studies (n= 2,317)

	Effects varying by age of depression onset			
	Onset age <15	Onset ages 15-25	Onset ages 26-35	Onset age ≥ 36
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
NSS	0.96 (0.71, 1.10)	0.97 (0.76, 1.25)	0.81 (0.63, 1.00)	1.26 (0.90, 1.76)

Note: All models controlled for age of the child when NSS were measured, race, sex, paternal socioeconomic status, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, ICU admission, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy

We performed an analysis to examine if NSS would predict current state depression in comparison to lifetime major depressive disorder, a measure that could be subject to recall bias. Current state depression was defined as having any depressive episode within the last year. There was no association between NSS and current state depression (OR = 1, (CI=0.8,1.1)) (Supplemental Table 3.6)

Discussion

This study used data from the NEFS project, a series of follow up studies of the adult offspring of the Providence and Boston CPP cohort. Our analysis provided a uniqe opportunity to study the association of NSS specifically with major depressive disorder across different stages of the life cycle, using a longitudinal design, where NSS were measured in childhood and lifetime major depressive disorder was measured using a standardaized instrument in a community sample.

Our data did not show an association between NSS measured at age 7 and risk of lifetime major depressive disorder or suicidal ideations or attempts. Our findings are consistent with results from prior studies that have failed to find an association between NSS and major depressive disorder (Boks et al., 2004; Zhao et al., 2013).

These findings do not support the notion that facing the challenges imposed by having NSS increases the later development of depressive disorders. However, evidence from longitudinal studies found higher levels of depressive symptoms in adolescents who had delayed developmental milestones in early childhood (North, Wild Tc Fau - Zwaigenbaum, Zwaigenbaum L Fau - Colman, & Colman) and others have also shown that children with disordered neurodevelopment are at increased risk for adolescent affective disorder (van Os, Jones, Lewis, Wadsworth, & Murray, 1997). Therefore, we tested the hypothesis that NSS would increase the risk of major depressive disorder specifically in childhood and adolescence. These critical periods are the times when they are struggling the most dealing with these deficits and are vulnerable to other adversities. However, if these deficits don't affect their emotional wellbeing during this period, then the risk of depression would decrease or dissipate. For instance, if they were surrounded with support systems that help them navigate these deficits

until NSS decrease, or if their ability to manage their deficits continues into adulthood. Our results did not support such hypothesis; we found no association between NSS and major depressive disorder in childhood relative to adolescence or adulthood. It is possible that having NSS in childhood impose some deficits, but the impact of these deficits on emotional wellbeing are not significant enough to cause major depressive disorder at any stage of the life cycle. It is also possible that NSS and major depressive disorder are neurobiologicaly different.

We used lifetime major depressive disorder as our outcome measure; lifetime measures are commonly used to study the prevalence of mental disorders in population surveys (Fergusson & Horwood, 2001; Kessler et al., 2012; Kessler et al., 2005; Kessler et al., 1994) and therefore are susceptible to recall bias (Patten et al., 2012; Thompson, Bogner, Coyne, Gallo, & Eaton, 2004) and possibly underestimating the prevalence of common psychiatric disorders compared to cumulative prospective reports (Moffitt et al., 2010; Olino et al., 2012; Takayanagi et al., 2014). However, there was no association between NSS and current state depression, a measure that is unlikely to be affected by recall bias.

Depression is a neuropsychiatric disorder, environmental and genetic factors can affect the maturation of brain circuits involved in affective function during the critical period of childhood and, ultimately, increase vulnerability for depression later in life (Ansorge, Hen, & Gingrich, 2007). When examining the neurological basis of depression, many studies focused on intelligence as a measure of neurological functioning (Koenen et al., 2009), rather than actual neurological deficits. However, the relationship between cognitive abilities and depression remains undetermined. Some studies have shown that lower childhood IQ was associated with increased risk of childhood and adult depression and was associated with greater comorbidity and long-term vulnerability for prolonged and severe depression (Hung et al., 2015; Koenen et

al., 2009; van Os et al., 1997). Others found that cognitive deficits do not serve as trait markers for developing depression but appear to be symptomatic of current disorder or clinical state (Douglas & Porter, 2009; Micco et al., 2009). Therefore, we chose not to control for cognitive abilities in childhood in our analysis. Furthermore, low cognitive scores were found to be consequences of NSS (Alamiri, 2016; Breslau et al., 2000) and therefore, can not be considered a confounder. However, our analysis controlled for many potential confounders not previously controlled for, such as factors suggestive of brain injury and abbarent neurodevelopment, in addition to commonly known confounders such as SES, race, sex and age.

The depressive syndrome is extremely heterogeneous, with the understanding that biological systems are more relavent in severe depression versus mild and moderate depression (Fournier et al., 2010). Although we did not examine the association between NSS and more severe subtypes of depression, we examined the association between NSS and outcomes of severity such as suicidal ideation and attempts. Our measure of MDD that is based on DSM-IV-TR (Association, 2000) has its limitations, where the MDD diagnosis encompasses a wide array of symptoms that overlap between different subtypes with different clinical course and prognosis. Simultaneously, it fails to detect equally disabling and possibly etiologically related syndromes that fall short of the threshold for diagnosis based on the criteria. Furthermore, we did not test for specific depressive symptoms that reflect disruption in biological systems like sleep and appetite disturbances.

As with other prospective cohort studies, our study could have been biased due to attrition. In our study the follow up cohort was only a fraction of the original sample; however, demographic variables and distribution of exposure and confounders were similar to that of the original sample (Supplemental Table 3.7).

The prevalence of MDD in our sample was 30% compared to 16.2% in the National Comorbidity Survey (NCS) (Kessler et al., 2003), and 13.1% in the Epidemiologic Catchment Area study (ECA) (Takayanagi et al., 2014). This sample is not comparable to other epidemiologic studies specifically recruited to study prevalence of psychiatric disorders. Our sample is a follow-up study of offspring of a pregnancy cohort, thus this sample is not a nationally representative sample in terms of the rates of psychiatric disorders. In addition, the association between NSS and depression is unlikely to be affected by the prevalence of depression in the sample. Arguably, the high prevalence of MDD may suggest that our sample is possibly a high-risk sample. This sample combined data from NEFS follow-up studies. Individual samples were stratified random samples from the entire cohort based on inclusion/exclusion criteria for each study. Some of these inclusion criteria are potential risk factors for depression, such as smoking (Boden, Fergusson, & Horwood, 2010) and learning disabilities but not pregnancy/delivery complications (Buka et al., 1993). Yet the prevalence of depression in the component studies ranged from 26% to 41%. This indicates that the high prevalence of depression is a characteristic of the entire sample regardless of the inclusion/exclusion criteria. In addition, in this analysis, we controlled for the study the offspring participated in.

In summary, NSS, manifestations of a minor cerebral dysfunction caused by either brain injury or aberrant neurodevelopment, were not found to be associated with the risk of lifetime depressive disorder at any stage of the life cycle, or with outcomes of severity. These results are based on our analyses that utilized a longitudinal design and controlled for a wide range of confounders. This suggests that the effect of NSS on self-esteem and emotional wellbeing are not

significant enough to cause clinical depression. In addition, our results, alongside prior evidence, does not support that NSS and depression are neurobiologicaly related.

Supplemental Material

Supplemental Table 3. 6 The distribution and association of current state depression by count of neurological soft signs in the New England Family Studies (n=2,317)

	Current state depression	
	% (n)	OR (95% CI)
NSS count		1.0 (0.8, 1.1)
0	18.54 (315)	
1	17.84 (96)	
2+	22.50(18)	

Note: All models controlled for age of the child when NSS were measured, age of interview, age of onset, race, sex, paternal socioeconomic status, birth weight, study site, pregnancy and delivery complications, Apgar scores at 1 and 5 minutes, resuscitation at birth, ICU admission, maternal history of psychiatric and neurologic disorders, maternal smoking, and exposure to drugs during pregnancy

Supplemental Table 3. 7 A comparison between the CPP sample that underwent neurological exam at age 7, the Boston and Providence branch, and the complete case analysis in key demographic variables and exposure distribution

	Sample: all children with neurological exam at age 7 (n = 41,911)	Sample: Children with neurological exam at age 7 from Boston and Providence only (n = 11,076)	Sample: NEFS participants (n= 2,317)
	Prevalence %	Prevalence %	Prevalence %
Female	49.5	48.9	53.4
Male	50.6	51.1	46.6
Birth weight < 2.5 Kg	9.3	8.0	9.2
SES			
High	23.5	35.4	27.9
Medium	49.2	50.6	51.1
Low	24.8	14.0	21.0

Prevalence of one or more	32.1	28.87	26.7
NSS			
Motor			
Ataxia	0.3	0.6	0.1
Dysdiadochokinesia	2.8	4.3	2.2
Dysmetria	0.6	1.3	0.8
Awkwardness	0.04	0.03	0.0
Sensory			
Astereognosis	1.1	0.7	0.8
R-L identification	26.0	21.6	22.2
Involuntary movement			
Mirror movement	2.1	3.0	1.9
Tremor	0.4	0.9	0.4

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